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„FOXP2 and the Hunt For a Language Gene“

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Language, genes and language genes

1.1 Linguistics and life sciences

In covering all aspects of language structure, use and origin, linguistics is hard to define by classical scientific categories. When the objective of research is the investigation of communication and its impact on the relationship between speaker and hearer or when it deals with language usage in a social group, it is undoubtedly a social science. Research on language as a cultural property is within the realm of humanities, while investigations of language disorders or language processing in the brain would qualify it as a natural science. This intrinsic interdisciplinarity accounts for the manifold ties between linguistics and related disciplines. Language is necessarily linked to a physical basis and cannot be seen as completely detached

from it. A relationship between language and natural science can be found in a number of disciplines, from the acoustical analysis of speech sounds on the basis of propagating waves in the air to mathematical models of neural circuits representing building blocks of language. The strongest and most apparent link, however, exists between language and its biological „hardware“.

In the present context, this relationship is of particular importance. In the last decades, mainstream linguistic theory has adopted a “biolinguistic” perspective. With the rise of cognitivism in linguistic theory, brought about mainly by Noam Chomsky, many parallels between language and natural sciences have been postulated, e.g. the existence of a “language organ” (Chomsky, 1965; Pinker, 1994). This is supposed to be an autonomous part of human cognitive abilities, but is not only seen as a theoretical concept, but as a biological entity. By stating this, linguistic theory not only tries to define a system to describe language per se, e.g. possible combinations of building blocks to allow for the generation of complex sentences, but – from observations of language structure and pathologies – makes predictions about biological foundations. Here, linguists enter a field where they lack the necessary methodology to prove these concepts and thus confirmation of these hypotheses has to come from biological experiments. Usually, this is not achieved by interdisciplinary researchers covering both disciplines, but by independent lines of research focusing on the same question from different perspectives and with very diverse methodology. The different approaches then have to be compared to evaluate the validity of the concepts.

This holds not only true for the aforementioned postulation of a language organ in the brain, but for every point of overlap between linguistics and life sciences. In this section, I want to outline general areas of biology that are linked to linguistic research and thereby require an interdisciplinary perspective.

1.1.1 Anatomy

The first and fundamental question in the relationship between language and the human body is the mere anatomical localization. While there is no doubt that

language ability must be associated with the brain, its exact organization has always been subject of research. This is not only a relevant question in terms of the macroarchitecture of the brain and the localization of language-related processing to a certain hemisphere, lobe, gyrus etc., but also on the level of the microarchitecture. The layering of the cortex, the organization of neurons and the types of connections formed might play a role or be specific to "language regions" in the brain. Since the function of the brain relies heavily on the interconnectedness of different cortical and subcortical regions, thinking about brain areas with distinct functions attributable to local neuronal networks will probably have to be abandoned in favor of a multidimensional view of cerebral organization. In section 2 of this chapter, evidence regarding the processing of language in the brain will be covered and theoretical considerations about the "localizability" of language competence will be discussed.

1.1.2 Genetics

The search for the "heritable element" has been an important issue in biology for a long time and in part still is an open question today. Although since the beginning of the 20th century genes – functioning as these heritable elements – are known to be stretches on a long, linear molecule (desoxyribonucleic acid – DNA) organized in structures known as chromosomes, certain information is also passed on to the next generation of a cell or an organism by different means, namely on the RNA or the protein level or by DNA modifications. This is another example for the enormous complexity of inheritance, but still leaves the genes as the main building blocks of information storage.

Especially when assuming an inborn language faculty, the study of genes and their regulation as the key players in the formation of a mature organism are intrinsically linked to research and theories on human language ability. Known associations between genetic abnormalities and language disorders, like in the case of Down or Williams syndrome, attest the direct influence of genetics on cognitive functions.

1.1.3 Developmental biology

The principal question in developmental biology is how a highly structured, multicellular organism is formed from a single cell. Various complex regulatory networks determine the fate of every single progeny of the fertilized egg to finally become a fully differentiated cell of the body exerting very specific functions, like blood, muscle, liver and nerve cells. Naturally, these processes have to be tightly controlled, since deviations from the correct plan will result in severe dysfunctions. From all organs of the body, the development of the nervous system is arguably the most complex, with regard to the formation of cellular processes to distant parts of the body as well as to the organization of the central nervous system. Language competence is based on this physical substrate and – if at least to some extent innate – has to be part of an inbuilt "cerebral construction plan". In any case, a certain human-specific predisposition to language learning has to be assumed and at least this – as the starting point of language acquisition – has to be integrated in a developmental plan and relies on its correct realization.

1.1.4 Evolution

After the publication of Charles Darwin's work "On the origin of species", the theory of evolution by natural selection gradually became the leading paradigm in looking at the history of man. Along with other human-specific traits, the ability to learn and use a complex sign system originated at some point in this process. Research has tried to shed light on both the time point and on the mechanism by which human language evolved. For the latter, several approaches have been used to find an explanation: On the one hand, "internal" explanations were formulated, which describe a gradual transition from an animal-like communication system based on a limited number of sounds to a more complex, elaborate system that – in the end – allowed the transmission of information from the speaker to the hearer in the form of a novel utterance – i.e. a combination of sounds that had not been part of the linguistic input of either of the two before (Bickerton, 2007). For a theory of this "evolution", no reference would have to be made to changes in the biological hardware, but since most of modern linguistic theory assumes a human specific

language module as the physical basis for language ability (e.g. Pinker, 1994; Hauser et al., 2002; Pinker & Jackendoff, 2005), biologists should – in principle – be able to trace this step in the evolution from non-speaking to speaking humans. Most major changes in the evolution of a species are not monofactorial, so it will often not be possible to pin down e.g. a change in brain morphology to a single molecular event. This can be expected even less for something as complex as the introduction of a new way of communication, but even in this case it should be possible to identify changes at the molecular level that parallel the "macroscopic" development and could also be functionally linked to the latter. Genetic changes are the most likely candidates for such an approach and their relevance to questions of the evolution of language – or more general communication systems – will be discussed later.

1.2 Language in the brain

To lay the ground for a discussion of the genetic background of linguistic abilities, I will first present the findings linking certain brain regions to distinct subdomains of language competence. Through the history of this discipline, different approaches and techniques have been employed to elucidate these questions. Already in the 19th century, certain areas were identified as necessary for language production or comprehension (1.2.1). With the technological advances made throughout the 20th century, a finer analysis of the neural substrate for language processing was possible, which revealed an even higher complexity than previously anticipated (1.2.2). Based on these findings, researchers tried to map very specific linguistic abilities to certain brain structures and postulated theories about neuronal mechanisms of language processing in the brain (1.2.3).

1.2.1 Autopsy studies

Since the beginning of research on language in the brain, researchers were divided if a localization of specific cognitive abilities is in theory possible (Obler & Gjerlow,

1999), i.e. if certain brain areas are associated with clearly defined functions, e.g. language, and consequently specific impairments would arise from lesions in this region (localizationists) or if large parts of the brain act together and no areas clearly dominant for language processing can be identified (holists, connectionists, interactionists). Advocates of the latter framework ascribe the major importance to the interaction of language with other cognitive abilities like memory or abstract thinking. Consequently, holists deny the existence of specific impairments in the sense of clearly defined and comparable syndromes, but argue for a single syndrome with different severity and characteristics.

The first attempts to map certain cognitive functions to distinct brain regions were undertaken in the late 18^{th} century, when Franz-Josef Gall tried to correlate anatomical peculiarities – e.g. "bumps" in the head – with exceptional cognitive abilities in certain fields, which was thought to be the consequence of an enlargement in the corresponding brain region (Gall, 1798). This discipline became known as phrenology. In people with outstanding language skills he observed protruding eyeballs and following his theory he reasoned that the underlying brain region was unusually big and the center for language in the brain. Following Gall, for a long time language ability in the brain was supposed to be located in the frontal lobe (Dronkers et al., 2000).

Scientifically founded experimental investigations trying to elucidate the organization of the brain originated from the observation of brain-damaged patients. Their impairments were thoroughly studied, and after the patient was deceased, his or her brain was examined to find morphological correlates of the observed (cognitive) deficits (cf. Libben, 2005). Two famous examples for these so called autopsy studies mark a milestone in the understanding of the organization of language in the brain and are still probably the most influential studies in this field.

In 1860, the French neurologist Paul Broca reports the case of a patient whose only utterance was the one syllable that became his nickname: Tan (Broca, 1861). At the same time, language comprehension seemed to be largely unaffected. A *post mortem* investigation of the patient's brain revealed a lesion in the inferior frontal lobe, which Broca correlated with Tan's language deficits. This area was later

defined as comprising Brodmann areas 44 and 45 and became known as Broca's area. Following Gall's dogma of the anterior localization of language, he was mainly interested in frontal lobe lesions and disregarded other areas that also exhibited abnormalities and might have been just as responsible for Tan's language deficits as the lesion in Broca's area (Dronkers et al., 2000).

Since the disorder Broca described did not just abolish language ability, but rather affected certain modalities or aspects of language use, this work was also the first step away from a model assuming one language center in the brain. Additional evidence for multiple language areas in the brain came from the German physician Carl Wernicke. In two patients he observed difficulties with language use that were very distinct – both symptomatically and anatomically – from patients suffering from Broca's aphasia (Wernicke, 1874). While for the latter ones the main difficulty was to produce comprehensible and syntactically correct sentences, Wernicke's patients were very fluent, but their linguistic output was filled with nonsense words. After *post mortem* investigations of the brain he concluded that this impairment correlated with a brain damage affecting the posterior part of the superior temporal gyrus. This area was then termed Wernicke's area and damage to this area was believed to result in "receptive" aphasia while Broca's aphasia was seen as an "expressive" disorder (Dronkers et al., 2000).

From the postulation of two distinct language centers, Wernicke concluded that also the connection between these two must be functionally relevant and hence damage to it should evoke specific and predictable symptoms (Wernicke, 1874), a syndrome that became known as conduction aphasia.

Aphasia studies are the classical and in part still employed method to obtain information about the function of a brain region, but the often extensive size of the lesions makes a localization difficult. This can to some extent be overcome by comparing the lesioned areas in patients with similar symptoms to narrow down the localization of the affected process (Dronkers et al., 2000). The variability in the cortical organization of the postulated language centers (Grodzinsky, 2006) and the categorization of patients on the basis of the clinical impression and test batteries, which are often not suitable for the identification of the nature of the language deficits in linguistic terms (Hagoort, 2006), also constitute problems in

this respect. In addition, in some cases (17% according to Basso et al. (1985)) the type of aphasia and the site of the lesion do not match, e.g. when the lesions are localized to posterior regions of the brain with a spared frontal lobe, but nonetheless symptoms associated with Broca's aphasia.

In general, the complexity of aphasic symptoms makes the localization of distinct processes difficult, since they never appear isolated, but always as part of a complex of impairments and compensatory mechanisms like reorganization of abilities in the brain, as Caplan et al. (2004) note when they characterize "aphasic performances [...] as the result of normal function, minus functional deficits, plus compensation" (p. 64).

1.2.2 Functional neuroanatomy (fMRI, EEG, PET)

During most of the history of these localization studies, researchers were dependent on *post mortem* examinations of brain-damaged patients (autopsy studies). In the last decades, electrophysiological and brain imaging techniques produced novel insights into language processing in the healthy brain *in vivo*. Investigations into functional neuroanatomy has led to more detailed information about the organization of language in the (healthy) brain, but also limitations of localization studies became apparent. In many cases, it is not one small region, to which a certain function in speech processing can be attributed, but many parts of the brain working together. Imaging techniques usually reveal changes in activation patterns over great parts of the brain that are thought to be specific to the task that was used to elicit them. In the following I will present the most common techniques and discuss some key findings concerning the localization of language in the brain.

In computertomographical investigations, so called CT scanning, repetitive x-ray images of brain sections are used to build up a three dimensional model of the brain. This has the obvious advantage, that it can be performed while the patient is still alive, but it nevertheless produces only a static image and its explanatory power is dependent on the presence of gross anatomical abnormalities that are visible in the CT images. In this sense, it is just an additional method for the evaluation

of the effect of brain lesions. For functional neuroanatomy of the living, healthy brain, approaches are needed that provide good time resolution and allow for the observation of brain activity in the course of performing a cognitive – in this case linguistic – task. Several methods have been developed to monitor brain activity (Libben, 2005; Lee et al., 2006; Rodden & Stemmer, 2008):

- Injection of radioactively labeled glucose in an artery and subsequent tracing of this compound is used in Positron emission tomography (PET). Cells in active brain regions consume more glucose than in the rest of the brain, which corresponds to an accumulation of the radioactive tracer in these regions that can be detected and visualized (cf. Horwitz & Wise, 2008).

- An alternative that does not require the use of radioactivity is to measure blood oxygen levels by detecting iron atoms of hemoglobin found in red blood cells. Oxygen molecules transported in the blood are linked to these iron atoms, and if this link is broken, hemoglobin's magnetic properties change (Pauling & Coryell, 1936). This is more often the case when the cells in the respective tissue are active and need oxygen as a component of energy producing cellular metabolism, leading to increased local blood flow. These hemodynamic differences can be detected, based on the different magnetic properties of iron with or without bound oxygen, using magnetic fields, and devices that generate magnetic fields of increasing strength are used to reach the highest possible resolution. Using this method, termed functional magnetic resonance imaging (fMRI), shorter acquisition times than in PET are possible, resulting in a better temporal resolution (cf. Hasson & Small, 2008).

- An even better time resolution can be achieved by a relatively new method, magnetoencephalography (MEG). Unlike electroencephalography (EEG), magnetic fields created by neuronal activity instead of the electric pulses are measured. In contrast to EEG, the signal is not affected by anatomical structures, but it is – on the other hand – very weak, and external influences (e.g. coming from the heart's magnetic field or the body's environment) on the local magnetic field have to be filtered out (http://www.psychologie.uni-regensburg.de/Greenlee/lehre/ws06/ Hauptstudium/MEG.pdf).

For every investigation of cerebral activity, it has to be taken into account that there is always activity in the brain, which might mask the neuronal activation elicited specifically by the task performed by the subject. Therefore basal activity of the brain has to be carefully measured in the form of minimal pairs and has to be subtracted from the activation pattern obtained during the test condition in order to get information about the specific contribution of the task (cf. Rodden & Stemmer, 2008).

In the last decades, imaging techniques have led to an enormous increase in the data on the localization of language processing in the brain. Apart from the classical speech areas and regions whose activation is explained e.g. by the process of articulation like the motor cortex, activation in wide parts of the cortex have been associated with language specific processing. Moreover, the role of individual language-relevant areas does not appear as clearly confined as in theoretical models based on lesion studies. The posterior inferior frontal cortex for example (which comprises also Broca's area) has not only been implicated in the processing of syntactic information as expected from the classical model, but also in tasks involving semantic decisions (Hirshorn & Thompson-Schill, 2006). An interesting dissociation has been described by Tranel and coworkers (2005) who observed different activation patterns in the left infero-temporal region in a naming task. If the target word was a tool, a more posterior activation was observed than in the case were participants were presented with an animal. Interestingly, this difference only exists between different categories of target words, but not between modalities: visual presentation and auditory presentation (of the noise the animal or tool characteristically makes) led to the same activation patterns in this region.

In principle, imaging studies have great potential to reveal which areas are involved in performing a specific task. On the other hand, they cannot provide information on which of these areas are necessary for this (and maybe only for this) task. Here, autopsy studies have more explanatory power and complement the information on brain activation patterns (Lee et al., 2006).

1.2.3 Organization of language in the brain – basic concepts

To achieve the ultimate goal of not only being able to describe the gross cortical organization of language but to ascribe distinct, e.g. syntactic processes to certain well defined areas, a number of assumptions have to be made, which Grodzinsky and Friederici (2006) summarize in the Syntacto-topic conjecture:

- major syntactic operations have a cortical equivalent
- the organization of these operations in the brain is linguistically relevant

This hypothesis states that the way syntax is organized in the brain is meaningful with respect to a certain linguistic theory. This theory thus would be corroborated by neuroanatomy. Whether it will be possible to uphold this implication of the conjecture in the face of diverging empirical data is questionable, but its fundamental principles underlie all localization studies.

The basic question about the organization of language in the brain deals with its division into two – macroanatomically – identical hemispheres. Are both sides equally important for language processing? Are the same language centers present on both hemispheres, are they divided up between the two or is language competence restricted to only one? Broca observed, that most of the patients with the language deficits observed by him suffered also from hemiplegia of the right body half (Broca, 1861). Given the crossing of nerve fibers and the subsequent control of one body half by the contralateral brain hemisphere, this argues strongly for a lateralization of linguistic abilities with the left hemisphere being dominant. Since Broca and the work of Norman Geschwind (e.g. Geschwind & Levitsky, 1968) many other studies have shown lateralization for most cognitive abilities, and indeed, in most of the patients, language processing on the level of grammar and meaning has been mapped to the left hemisphere in the majority of individuals tested. Other language relevant domains, however, like pragmatics and prosody seem to be localized preferentially in the right hemisphere (cf. Libben, 2005). Since language cannot be seen as one uniform "skill", the question about the lateralization of the brain with respect to linguistic abilities can only be addressed for individual subsystems.

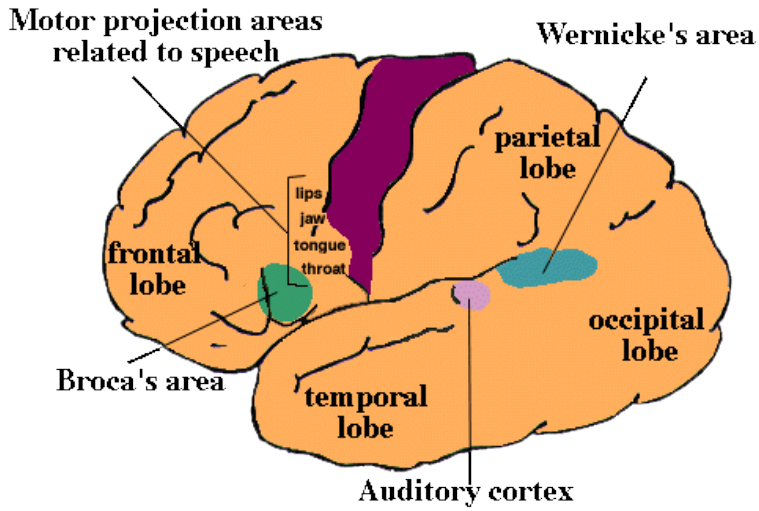

Figure 1.1: Classical model of language organization in the brain. (http://www-rohan.sdsu.edu/~gawron/intro/course_core/lectures/aphasia_cases_slides.html; accessed 24.3.2013)?

Work on the localization of specific linguistic abilities has been presented in the preceding two sections. A wealth of so called "language centers" have been found (cf. Fig. 1.1), but this information on its own has very limited explanatory power. The cooperation of these individual units has to be elucidated in order to get a basic understanding about more complex linguistic tasks as posited even by the most simple sentence. Starting with the work of Carl Wernicke (1874), the question of the interconnectedness of the different brain regions that had been identified as necessary for intact language production and comprehension arose. Based on the findings of 19th century localizationists and on later aphasia studies a theory has been formulated concerning the division of tasks between the different areas and their concerted action that leads to what could be called a successful speech act, from both sides, the hearer and the speaker (Geschwind, 1967). The resulting theory is known as the classic Broca-Wernicke-Lichtheim-Geschwind model, which shaped the view of language in the brain for most of the time of its investigation (Shalom & Poeppel, 2008): A basic triangular organization scheme of language in the brain is assumed, consisting of a motor processing area, an auditory processing

area and a conceptual area, whose localization is unknown and either considered to be diffuse (Lichtheim, 1885) or spatially defined (Geschwind, 1967). Evidence for the latter comes for example from a patient, who was unable to understand or utter even the simplest linguistic elements, but was doing well in repetition and could even produce learned phonetic patterns like a short poem without prior presentation (Geschwind et al., 1968). *Post mortem* investigations showed that all known language areas had been spared, but connections with the rest of the brain had been disrupted by the lesion. The patient was therefore unable to link information from other parts of the brain – among others, the postulated conceptual center – to the speech areas. Lesions in any component or connection in this triangular system (Fig. 1.2) was predicted to account for the seven main aphasic syndromes (Caplan & Utman, 1994).

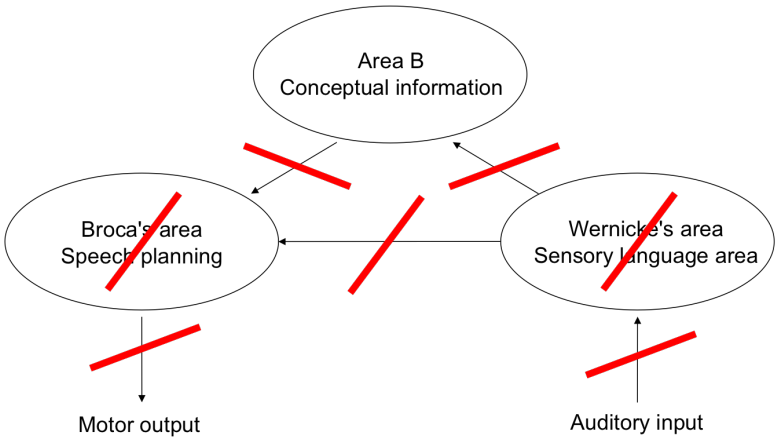

Figure 1.2: Broca-Wernicke-Lichtheim-Geschwind model of language processing in the brain. Red lines indicate the positioning of lesions leading to the seven main aphasic syndromes.

Many later approaches built on the classical model and suggested modifications in terms of localization and the mechanisms of processing (Shalom & Poeppel, 2008). Friederici (2002), for example, divides the aspects of syntactic and semantic identification and the construction of relations between them to temporal and frontal areas, respectively, and thus leaves the level of single words as the targets of processing in the brain. Indefrey and Levelt (2004) base their model on the

timing of individual steps in the production of words and make conclusions about the functional anatomy of active brain regions.

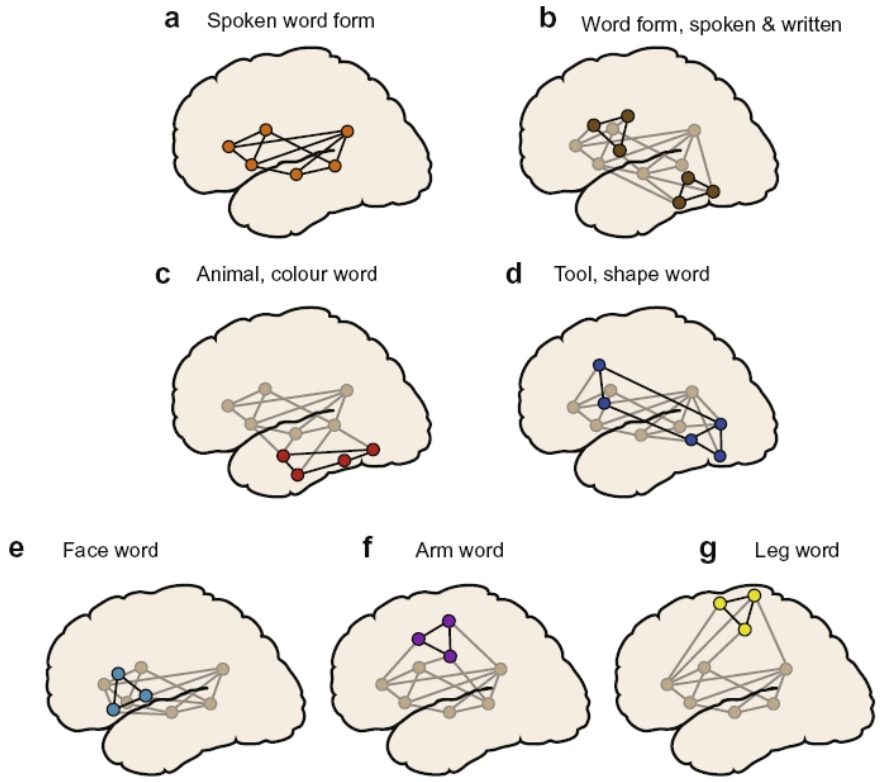

Figure 1.3: Cortical networks extracted from activation patterns of word processing. The activation of different groups of neurons depends on the modality and the sematic content, resulting in characteristic activation patterns for individual semantic categories correlating — in the case of words referring to body parts — to the motor area controlling these regions (from Pulvermüller et al., 2009, Fig. 5).

As more and more information is accumulated about the interconnectedness and separability of individual "language centers", the partly autonomous nature of processing areas for different tasks, as implied in the classical model and more recent frameworks building on it, becomes more difficult to maintain (Pulvermüller et al., 2009). In addition, the question if language processing in the brain occurs in a parallel or serial fashion, with fast reaction times arguing against pure serial

models and delays in the activation times of different cortical areas against purely parallel processing with no interdependences, can best be explained and resolved with a model of cortical circuits as the representations of distinct linguistic tasks (cf. Pulvermüller et al., 2009 and Fig. 1.3).

Trying to incorporate conclusions from the numerous imaging studies conducted to find individual activation patterns for specific linguistic tasks into a general theory of language processing leads to the postulation of ever more complex models, that cannot be covered here. In some instances, different studies yield – at least seemingly – contradictory results, which might be due to experimental differences, but still pose a problem for a unified account of language processing in the brain.

Taken together, it becomes more and more clear that attempts to purely map language onto brain structures will not help to gain a real understanding of the underlying biological processes. Therefore, other levels of explanation, which are not purely descriptive, attract growing attention. One of these fields is the study of links between the genetic endowment and linguistic abilities.

1.3 Language and genetics

As in the case of many other diseases, for some language disorders clear patterns of inheritance have been observed (cf. Gibson & Gruen, 2008). This applies e.g. to specific language impairment (SLI), which shows 45% concordance between siblings and 90% between twins. This is generally considered to be evidence for simple genetic inheritance and – in the easiest case – consequence of a mutation in one genetic locus. In cases like Down syndrome or Williams syndrome, where the observed phenotype does not have a monogenetic cause, but is associated with regional chromosomal deletions or rearrangements, the cause of the symptoms can be mapped very well on the genome, but little functional conclusions can be drawn due to the involvement of multiple genes located within the affected region. To identify individual genes necessary for human language ability and to shed light on their functional contribution, however, it would be desirable to find mutations

linked to a specific impairment of language processing with – in the best case – otherwise unaffected cognitive abilities.

Before I will go into the details of the relationship between language and the brain I will give an overview about the biological basis necessary for the evaluation of the interplay between specific changes in the genetic information and language impairments.

1.3.1 Genome organization and DNA mutations

1.3.1.1 DNA and gene expression

The heritable information of any organism is encoded and passed on to the next generation in the form of a four letter code: A, T, G and C are abbreviations for the 4 molecules Adenin, Thymin, Guanin and Cytosin. These four bases are the core components of desoxyribonucleic acid (DNA), which forms a linear polymer of single units (nucleotides), a chromosome. In the nucleus of any human somatic cell (except erythrocytes), 2 sets of 23 chromosomes are present, with a total of approximately 2x 3 billion nucleotides. Therefore, the human genetic information is a 3 billion letter sequence of A, T, G and C.

A surprisingly small part of this genome (in humans approximately 1.5%) constitutes coding regions of genes (Lander et al., 2001), stretches of DNA that eventually serve as blueprints for most cellular components. The process by which information from DNA is transformed into ribonucleic acid (RNA), the "mobile" form of DNA, which sometimes can also exert cellular functions on its own, and proteins, is called gene expression. In the majority of cases, proteins are the most important "gene products", serving manifold functions like catalyzing chemical reactions e.g. in the degradation of nutrients (enzymes), representing building blocks for the cytoskeleton or other cellular structures or serving as a component of cellular signal transduction cascades, which help the cell e.g. to react to changes in its environment.

The DNA sequence of a gene determines the amino acids the resulting protein is made of, but it also controls under what circumstances the gene is expressed, i.e. the corresponding RNA and protein are produced. Regulatory sequences can inhibit or enhance gene expression or alter the amino acid sequence of the resulting protein, depending on various components like specialized proteins recognizing and binding these areas, so called transcription factors. This is achieved e.g. by changes in the structural organization of the DNA, thereby facilitating or preventing access of the molecular machinery necessary for gene expression.

1.3.1.2 Mutations

Despite a number of control mechanisms that have evolved in the history of life, changes in the DNA sequence, the genetic information, occur at a certain rate. It is mostly during replication of the whole genome preceding cell division that errors in the replication machinery lead to so called mutations. Since most of human DNA does not have an obvious purpose, at least not on the level of single nucleotides, most of these mutations remain unnoticed and might only become important in situations like paternity tests or forensic screenings, since they constitute a characteristic fingerprint of the individual. But if the coding region of a gene (the part of it that constitutes the blueprint for the corresponding protein) or regulatory regions (that determine the conditions under which this gene is expressed) are affected, in many cases the mutation will not go unnoticed. In any case the type of mutation is crucial for the aftermath.

- **Point mutations** are single nucleotide replacements that might or might not alter the amino acid sequence of the resulting protein, depending on the exact environment. In the most dramatic case, a signal in the DNA sequence can be created that causes the premature termination of transcription (the process by which RNA is synthesized from the DNA template), ultimately leading to the production of a truncated (and sometimes deleterious) version of the protein.
- Three consecutive nucleotides in the coding region of a gene determine one amino acid in the corresponding protein. The information if a nucleotide is in

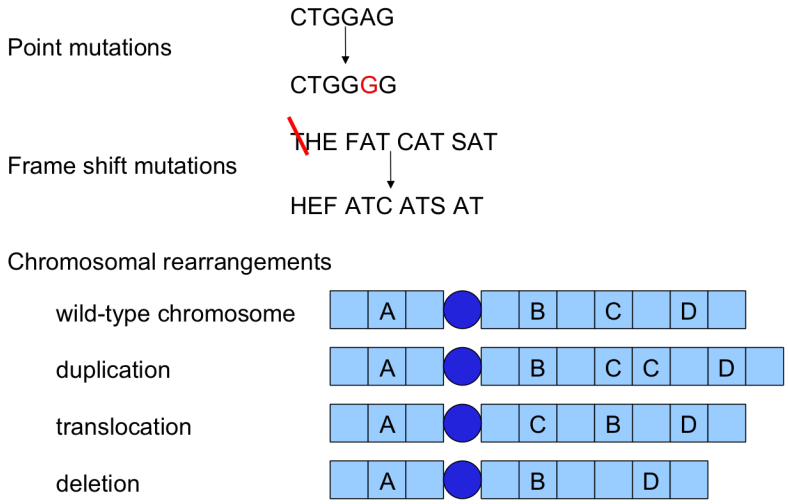

Figure 1.4: Types of genetic mutations on the level of individual nucleotides (top, example taken from http://evolution.berkeley.edu/evolibrary/article/mutations_03) and large genomic regions (bottom).

first, second or third position of this triplet is crucial for the right amino acid to be incorporated into the nascent protein. Even single nucleotide deletions or insertions within the coding region of a gene therefore have an impact on the rest of the gene shifting the following triplets by one nucleotide. These so called **frame shift mutations**, despite affecting only one single nucleotide, have a fatal impact on the rest of the gene, leading to the production of a completely altered protein (Fig. 1.4).

- Apart from mutations on the level of single nucleotides, there are also large-scale mutations that usually affect a whole stretch of a chromosome, but can in principle also affect only one gene. Chromosomal reorganisations include **duplications**, **translocations** and **deletions**, which are presented in figure 1.4. There are many possible causes for these phenomena, and the consequences are equally manifold. While duplications usually lead to an overproduction of the proteins the affected genes are encoding and deletions have the opposite effect, the fate of a translocated chromosomal region is less clear. If it is inserted in an inactive region on a different chromosome, the affected

genes might be completely silenced, while insertion in a very active/heavily transcribed area will most likely lead to elevated levels of the proteins. The impacts of these events will not be restricted to the translocated genetic region, also the target site might be affected, e.g. by the random insertion which might lead to the disruption of a gene.

In general, mutations usually affect one of the two copies of a gene present in a cell. Depending on the gene, a malfunction in one copy might be completely complemented by the second, leading to no visible phenotype. It might as well lead to reduced levels of a (functional) gene product, which may or may not cause problems for the individual, depending on the dosage sensitivity of the cell in the case of the respective protein. In the most drastic case of a dominant effect, the second copy is either non-functional (silenced, carrying a mutation itself etc.) or the aberrant gene product interferes with the normal action of the correct protein made from the unaffected copy of the gene.

1.3.1.3 Mapping a mutation: how to find the affected gene

In the case of a phenotype that can be assumed to have a (mono-)genetic cause, it is necessary to map the responsible mutation on the genome in order to find the affected gene. This can be achieved following several strategies.

In the case of large-scale mutations where large portions of a chromosome are duplicated, deleted or translocated, it can be possible to narrow the site of the change down at least to a specific chromosome arm by microscopic inspection (karyotype analysis). Although this will not give exact information about the genes involved, it will facilitate the following investigations. But for most mutation events, there are no such cues and localizing a point mutation in the whole genome of three billion nucleotides is like looking for a needle in a haystack.

The most important method for the localization of a specific mutation traditionally was linkage analysis. Here co-inheritance of the marker with certain phenotypical and genetic markers is quantified. If the mutation and the marker

are on two different chromosomes, they will not show unusually high rates of co-segregation in the next generation. If both are located on the same chromosome, this depends on the distance between the two, since during the production of germ cells, corresponding DNA stretches are exchanged between the two members of a chromosome pair, which happens less frequently when the two loci are in close physical proximity.

For mutations underlying human diseases, these linkage studies are dependent on the availability of a high number of affected and non-affected members of a family or of several families.

1.3.2 How to find a language gene

Before reporting specific associations between genetic variations and language impairments, I would like to discuss the general pathway to the identification of a language gene in this section.

When inheritance of a language deficit indicates genetic involvement, it is imperative to exclude external factors that might be responsible for the observed incidence of the defect in a particular environment. In this context, comparing concordance in monozygotic versus dizygotic twins can provide additional information: if siblings with the same genetic endowment have a higher chance to develop the deficit under investigation, factors in the environment alone cannot account for this (Farrer, 2004). If no obvious external factor can be identified, the first step to elucidating a possible genetic background is to conduct genetic analyses of affected and unaffected family members. The presence of genetic differences between the two groups would then support the hypothesis of a genetic involvement. These differences then have to be mapped and the mutation needs to be classified in order to be able to draw conclusions concerning its consequences (see previous section).

If only a smaller region of a chromosome is affected, the type of DNA sequence is of utmost importance: Does the mutation lie in a regulatory region, the coding region, or in a region with no known function? From the localization of the mutation

within a gene (using the term in a broader sense, comprising the coding sequence and all regulatory regions around the actually transcribed DNA segment) some assumption can be made how gene expression will be affected.

If the altered DNA segment is found to comprise only one gene, the question arises if its function is known or if there are at least strong bioinformatic hints, based on which its function can be predicted. Following the earlier considerations, in what way will the mutation affect this function? Can it be assumed that, for example, the resulting amino acid sequence of the corresponding protein will be changed in a way that makes proper execution of its function impossible? Or will changes in DNA sequences regulating the transcription or translation of the gene prevent its expression or lead to a massive – and probably fatal – overproduction?

In trying to identify a "language gene", it is not the primary goal to find genes that are necessary for the correct development or functioning of the whole organism and whose malfunction leads – among many other problems and probably as a side product – to language impairments. It would rather be preferable to hit upon a gene, for which a link to language processing in the brain can be identified. Is it brain specific – maybe even expressed in some areas and in others not – or is there a reason, why it would affect language in particular? At least with the current state of knowledge, it is probably not possible to answer the latter question, since it is not known if and in what respect language processing differs from other cognitive functions on the molecular level.

In general, investigations into the genetic basis of language ability suffer from a problem 19$^{\text{th}}$ century localizationists were also facing: both approaches are dependent on the investigation of pathologies. For investigations of language processing in the brain, the development of imaging techniques helped to overcome this limitation; in the hunt for a language gene, this transition to healthy individuals will not be possible in the near future, and even if the experimental feasibility will be ensured, manipulating the human genome will – hopefully – always be restricted by ethical concerns.

1.3.3 Language disorders linked to genetic alterations

In studying the genetic background of linguistic abilities, impairments in language competence or performance are linked to alterations in the genetic endowment of an affected individual. Here, a distinction has to be made concerning the usability of this association for the attribution of a specific function to this DNA region. If the genetic alteration is regional, i.e. extended stretches of DNA are affected by e.g. a deletion or duplication of a part of a chromosome, it will be difficult to attribute the observed phenotype to a particular gene. In the case, however, where only one or few genes are affected e.g. by a point mutation or a small-scale chromosome rearrangement, it might very well be possible to functionally link these "local" changes to the resulting cognitive deficits.

One of the most well-known and extreme cases of a regional genetic alteration affecting cognitive (including linguistic) abilities can be found in Down syndrome (trisomy 21). In contrast to the usual two sets of chromosomes, the genetic inventory of patients suffering from Down syndrome contains a third copy of chromosome 21 (hence the alternative designation trisomy 21).

Despite various medical problems and distinctive anatomical features and a mild to severe learning disability, patients suffer from language impairments, which are in most cases disproportionate to overall cognitive difficulties and are arguably not attributable to the learning disability alone (Laws & Bishop, 2004). This hypothesis is corroborated by other dissociations between language and general cognitive abilities, like in the case of Williams syndrome. Patients suffering from this disease show a deletion of an area on chromosome 7 where 26 known genes are located (Osborne & Mervis, 2007). This results in major physical deficits, e.g. cardiac and gastrointestinal problems, and cognitive impairments affecting social interaction and general intelligence, but – to a large extent – sparing language competence (cf. Bartke & Siegmüller, 2004).

These examples provide evidence for a language faculty in the brain that is independent of general cognitive abilities, but little information can be obtained as far as the specific involvement of individual genes is concerned. In general, large chromosomal alterations associated with language deficits – in combination with

what is already known about the affected genes – might reveal first hints which genes would be obvious candidates for a role in the evolution or the physical basis of language competence, but no direct conclusions concerning the nature of this involvement and the functional contributions can be drawn. In a system as complex as the human genome, the only possibility to break higher cognitive functions down into actual biological units is to investigate a specific alteration. In the following, I would like to present two cases, where research has come one step closer to this ideal situation.

1.3.3.1 Developmental dyslexia/Reading disorder

Dyslexia is traditionally seen as a „specific and significant impairment in reading abilities, unexplainable by any kind of deficit in general intelligence, learning opportunity, general motivation or sensory acuity“ (Critchley, 1979; cited in Habib, 2000, p. 2374), but more recently rather as a mild disorder in oral language, whose most obvious deficit concerns the acquisition of reading (Ramus, 2006). A co-occurrence rate of 44-77% among twins points towards the heritability and thus the genetic foundation of this disease (DeFries et al., 1987). Although these numbers argue undoubtedly for a heritable trait, environmental factors will still play an important role, since the percentage obtained in twin studies still indicates a possible dissociation between genotype and phenotype (Gibson & Gruen, 2008). When patients' brains were examined *post mortem*, abnormalities in neuronal migration have been found, which especially affected the left perisylvian region, an area associated with diverse linguistic skills (Galaburda et al., 1985). The relevance of this observation was corroborated by brain imaging studies showing alterations in the same cortical area. As a next step, genetic loci have been identified, mutations in which can potentially cause dyslexia (Grigorenko, 2003). In the following years, genes within these regions have been found that could be linked to the disease:

- In DCDC2 (Meng et al., 2005) the relevant mutation was shown to affect a regulatory region. Therefore, the phenotype is not caused by a change in the

protein, but rather by alterations in the spatial and temporal control of its expression and potentially also in the amount of protein produced.

- A mutation in KIAA0319 also affected a regulatory region, leading to decreased production of the respective messenger RNA (Cope et al., 2005)

- DYX1C1 was affected by a chromosome translocation (Taipale et al., 2003), but does not seem to be a factor sufficient for developing symptoms of dyslexia (Gibson & Gruen, 2008).

- ROBO1 is also affected by a DNA translocation in some affected individuals. It has been already previously shown that this gene is necessary for guidance of a growing axon to its target in the fruitfly Drosophila melanogaster, an important model organism for many developmental processes (Hannula-Jouppi et al., 2005). This function can be nicely linked to the observed deficits in dyslexia, whose underlying deficits might very well be incorrect neuronal wiring in specific parts of the brain.

Also for the other candidates, molecular functions could be identified. All three have been implicated in neuronal migration (Francis et al., 1999; Paracchini et al., 2006; Wang et al., 2006), making them necessary for the correct development of the cortex, whose cellular organization stems from controlled migration of neurons from the area where these cells originated to distinct cortical layers during embryonic development. The three corresponding gene products might be involved in different cellular functions during this process, but the impairment in neuronal migration following their malfunction points towards a necessary contribution of all three genes in specific brain regions (Ramus, 2006). One conceptual problem with this assumption comes from the fact that none of these three genes is restricted to the areas affected in the investigated individuals. Therefore, another molecular player is necessary to render this deficit specific to a language area rather than affecting the whole cortex resulting in general cognitive (and also motor and sensory) abilities. This might very well be a common mutation that occurs quite frequently within a given population and by itself does not lead to a noticable phenotypic change (a so called polymorphism), but in combination with a (specific) alteration

in the aforementioned candidate genes conveys the observed spatial restriction of the morphological phenotype (Gray et al., 2004; Ramus, 2006).

Apart from the four genes described above that are candidates for crucial factors for developmental dyslexia and thus for a (more or less) specific part of human language ability, also other genetic elements will come up as the investigation of chromosomal susceptibility regions for this disease progresses. With a growing number of factors found to be responsible for and involved in developing a certain disorder, the question arises how legitimate it is to call these "language genes", especially since they are not confined to the brain and will most probably be also involved in essential processes in other parts of the body (Ramus, 2006). This second aspect is a logical consequence of general properties of gene function, namely that the same protein can be involved in several processes in distinct parts of the body, and each of these functions – and the expression of the gene of interest – can be controlled by regulatory mechanisms in the respective tissue. The brain-specific function of this gene therefore needs to be seen independently from a possible role e.g. in lung, liver or intestine. This feature does not per se interfere with a possible crucial role in language processing and should not necessarily lead to its elimination from the list of "language gene"-candidates.

The mere number of genes found to cause a certain disorder does not pose a problem for the explanatory value of these findings for the understanding of language competence on a biological basis either. In general, genes are only the starting point and building blocks of a certain cellular process. Most of these processes, like metabolic pathways or the migration of a neuron, will depend on a large number of players. Leaving aside all additional factors that might be necessary to constrain the effect to a certain region of the brain, every necessary component of this complex event will thus potentially result in the same "macroscopic" deficit. Although it might not be possible to reconcile this with the view of a language gene as a single factor acting alone to enable humans to use language, it is reasonable to assume that a number of cellular processes will be at the basis of human language ability and interfering with these will result in more or less specific deficits. Thus, proving the necessity of such a pathway for language production or comprehension will not lead to the identification of "the" language gene, but will further

contribute to our understanding of the basis of cognitive functions on a single-cell level.

1.3.3.2 Specific Language Impairment

Specific language impairment (SLI) is defined as a "developmental disorder that selectively affects the domain of language processing" (Friederici, 2006, p. 946). Its manifestations potentially involve for example phonology, syntax or the comprehension of complex sentences (Marinis, 2011). In a general sense, this term is used for difficulties or delays in language acquisition that are not attributable to apparent internal (e.g. loss of hearing) or external (e.g. lack of linguistic input to the child) causes and do not correlate with general cognitive deficits or learning disabilities. As this potentially applies to a very diverse range of language problems, individual cases of SLI can vary a lot, and due to the heterogeneity of this symptom complex, estimates of the incidence in a population are broad, ranging from 3-8% of children (Tomblin et al., 1997). It has also not been possible to define clear subtypes since the manifestations of the disorder can be subject to changes over time.

Numerous hypotheses concerning the underlying deficit have been put forward, which aim to explain either a specific subtype of SLI or the common properties of these impairments (cf. Ullman & Pierpont, 2005; Marinis, 2011). Some of these theories attribute the impairments in SLI to a processing deficit that could be either general in form of a limitated general processing capacity (e.g. Leonard, 1998) or specific to a linguistic domain or modality, e.g. phonology (e.g. Gathercole, 2006). According to the computational complexity hypothesis, the deficits originate from the interfaces between language and other cognitive systems and an inability to access and integrate information of different kinds (Jakubowicz, 2003). Ullman and Pierpont (2005) propose a Procedural Deficit Hypothesis claiming that "SLI can be largely explained by the abnormal development of brain structures that constitute the procedural memory system" (p. 399). On the other hand, representational accounts posit a grammar specific deficit underlying the symptoms (Marinis, 2011). Here, certain subcomponents can be affected, e.g. deficits in specific mark-

ing (e.g. Wexler, 1998) or feature blindness (Gopnik & Crago, 1991), or the deficits can be relatively broad within the domain of grammatical processing (van der Lely et al., 1998; Ullman & Gopnik, 1999).

As far as the genetic background of SLI is concerned, many of the properties stated for developmental dyslexia also hold true here. A high degree of inheritance of certain traits in SLI evidences a clear genetic component (Bishop et al., 1995). Furthermore, also twin studies support this hypothesis (cf. Plomin et al., 2001). While monozygotic twins have 100% identity in their DNA sequence, for dizygotic twins this value is much lower, since they are not derived from the same event of fusion of the oocyte with a sperm and thus the parental contributions on the DNA level differ between them. If monozygotic twins show a higher concordance in a specific feature than dizygotic twins, it can be concluded that this is connected to the identity of their genomes. In contrast, same ratios between mono- and dizygotic twins point towards the involvement of a shared environmental factor that somehow causes the observed co-occurance of a trait (Hayiou-Thomas, 2008). In the case of SLI, differences between monozygotic (90% concordance) and dizygotic twins (45%) exclude a major contribution of environmental factors (Bishop, 2006), since environmental conditions will not be fundamentally different in this situation between mono- and dizygotic twins.

Although there is no doubt about the involvement of genetic factors, their identification turned out to be problematic. Potential regions of interest have been identified on various chromosomes, where mutations could be correlated with the occurrence of deficits classified as SLI (e.g. Bartlett et al., 2002; Villanueva et al., 2011). Looking at the diversity of the symptoms that are found in children diagnosed with SLI, it does not come as a surprise that many underlying genetic changes can be found. The deficits on the molecular level will be probably just as diverse as on the behavioral level. In addition, it is unclear, whether these different causes are all monogenetic, i.e. involving only one gene, or whether they are caused by an accumulation of mutations in several genes (or a large chromosomal rearrangement) that gives rise to the observed phenotype (cf. Bishop, 2009). Despite the lack of a one-to-one mapping of SLI onto a single gene, the link of specific cases of SLI to the malfunction of a particular gene, might – by comparison with the specific deficits

observed in the individual – lead to insights into its involvement in the processing of language in the brain. Research into this topic in recent years revealed that both types – mono- and multigenetically caused SLI – are present among the diverse incidences of this disease. One of the genes alterations in which where shown to correlate with performance in a specific language task (non-word repetition) is CNTNAP2 (Vernes et al., 2008), and deficits connected with mutations in this gene have also been reported for autism (Alarcon et al., 2008) and schizophrenia (Friedman et al., 2008). As in so many other cases, however, this will most likely only constitute one building block of the symptom complex.

Another remarkable property of investigations of the genetic background of language disorders is the apparent lack of one-to-one mapping between a phenotype and a genotype, but that diverse genetic alterations can result in – superficially – the same symptoms. This can be described with the concept of "canalization" (Waddington, 1942), implying that several changes on the molecular level feed into the same "macroscopic" impairment, as described earlier for different genes involved in pathfinding/cell migration and their potential causative role in reading disorder (cf. section 1.3.3.1). In addition, for an impairment to become evident and "testable", it might be necessary for different mutations to accumulate so that an overt deficit can be observed (Bishop, 2006), leading to a similar model as assumed for the emergence of cancer (Hanahan & Weinberg, 2000). Individual risk alleles for SLI, i.e. mutations potentially capable of causing a deficit in language processing, might have only very subtle effects, and only a co-occurence of more than one in an individual will have clinical importance. In these cases, it might be advantageous to investigate risk alleles and their bearers for small but potentially specific alterations than just restricting the research attention to clinically manifest cases (Bishop, 2009).

Since human language ability not only presupposes the cognitive capability to process an extraordinarily complex sign system and very efficient cortical networks for the processing of language tasks, also the anatomical necessities should not be overlooked. Much like the development of neural circuits, the formation of the physical organs producing spoken language depends on a complex network of biological processes. Although this aspect will probably not lead to a better

understanding of the intrinsic structure and organization of language in the brain, it can potentially contribute to the clarification of the species-specific nature of human language – which might in part simply be due to a lack of anatomical preconditions in other species. One candidate for this is a gene termed "tospeak" which Raymond Clark and colleagues have found in an inherited speech impairment caused by a malformed larynx. At the meeting of the American Society for Human Genetics in 2009, Clark presented a mutation in this gene as the underlying cause for the defects, since in this situation, it is not made into protein and thus cannot promote the expression of another gene, growth and differentiation factor 6 (GDF6), which, when mutated in mice, causes malformations in the larynx and joints that look similar to those seen in the family affected by the speech problem (http://blogs.nature.com/inthefield/2009/10/ashg_2009.html, accessed 10.2.2013). This potentially constitutes an example, where one gene modulates the activity of a global growth factor to guide its tissue specific activity and the formation of specific features.

These examples of genes implicated in language impairments illustrate the numerous attempts to find a causative link between language and genetics, but none of these has so far attracted as much attention as a point mutation identified in an English family. The gene affected by this mutation subsequently became the most popular candidate and synonym for a language gene and will be covered in the following chapter.

2

FOXP2 as a candidate for a language gene

2.1 The KE family

The search for genetic factors determining and underlying human language ability was greatly advanced by the description of an extended family, in which a language disorder can be followed over (by now) four generations and more than 15 affected individuals. This case was first described in 1990 (Hurst et al., 1990) and has attracted a lot of attention from various disciplines in the two decades since then. Although many cases of inheritance of a language impairment have been reported so far, the high number of individuals and the possibility to follow the disorder over four generations is still unique and made neuropsychological and neurolinguistic testing on a large scale possible.

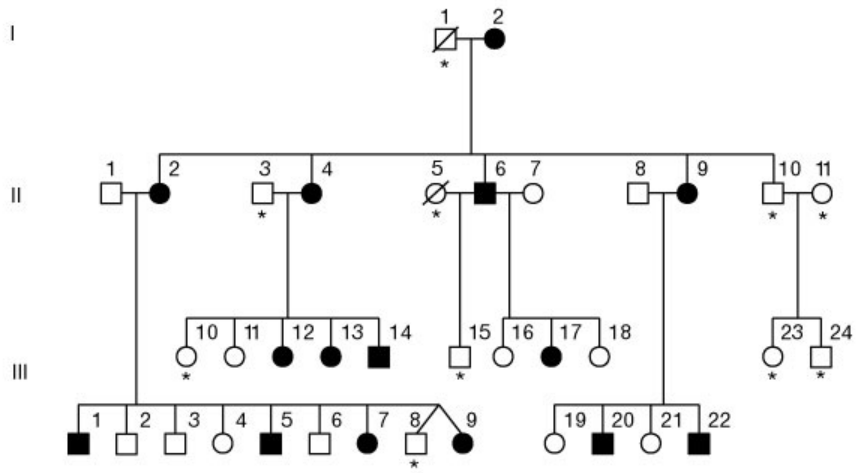

Figure 2.1: Pedigree of the KE family. Squares indicate males, circles females, affected individuals are represented by filled symbols and persons diseased at the time of investigations are crossed out (modified from Lai et al., 2001, Fig. 1).

A pedigree of the first three generations of the KE family is shown in Figure 2.1. Affected individuals can be found in every generation, and the pattern of inheritance seems to be a simple Mendelian segregation of a dominant feature (Hurst et al., 1990), i.e. the predisposition to developing the disorder is present on a single locus on one of the two homologous chromosomes. One of each pair of chromosomes is passed on to the child of the individual, irrespective of whether this is the chromosome carrying the predisposition or the wild type allele (chromosomal locus). Thus, on average half of the next generation can be expected to develop the disorder. The pedigree of the KE family resembles this pattern and therefore the disorder can be assumed to be monogenic (or caused by an alteration within a narrow region of one chromosome).

2.1.1 Linguistic deficits

Approximately half of the members of the KE family (16 out of 30 at the time of the first report) were diagnosed as dysphasic. The impairment of affected individuals

in the KE family was first described as developmental verbal dyspraxia (Hurst et al., 1990) i.e. an impairment in the control of movement and sequencing of orofacial muscles that can be observed during the development of the child, without a case of late onset of the symptoms. Their speech is unintelligible to the naïve listener, and they were taught a sign system to augment their speech and to facilitate interaction with their environment. Despite intensive speech therapy, affected individuals are still unintelligible over the phone and on tape (Vargha-Khadem et al., 1995). Language competence seems to improve over age, as all generations report that the impairment of their children had been much more severe at younger age. Gopnik and Crago (1991) explain this by stating that older subjects learn to find strategies to hide and balance their deficits – probably in part as a consequence of the extensive speech therapy that most of them received. The language deficits, however, are still apparent in tests.

In general, language production seems to be more severely affected than comprehension. Although the fine motor abilities of the orofacial musculature necessary for the precise production of speech sounds seem to be affected, no neurological deficits affecting limb movements and swallowing could be observed and also hearing seemed to be unimpaired (Hurst et al., 1990), ruling out an inability to perceive the input correctly as a source for the developmental dysphasic symptoms. Cognitive abilities other than language seemed to be affected as well, but in general to a smaller extent (Hurst et al., 1990; Lai et al., 2001), although this has been a matter of debate. It can also not be ruled out that some of these defects (especially in social interactions) are secondary effects to the inability to communicate with their environment, although the pragmatic aspects of language seem to be largely intact (Gopnik & Crago, 1991).

Subsequent to the initial description of the KE family, a number of researchers from various backgrounds tried to further characterize the deficits and find explanations for the impairments specific to language based on linguistic theory (cf. Vargha-Khadem et al., 1995).

Gopnik (1990), Gopnik and Crago (1991), Pinker (1991; 1994) and Jackendoff (1994) claim, that the deficit of the KE family is language specific, and even more precisely, that it stems from a deficit in specific grammatical abilities. Gopnik

(1990) performed investigations based on tests for aphasia and observed that while there was no significant difference in the performance of the affected individuals to the control group (healthy KE individuals) in tasks involving reflexives ("He washes him" versus "He washes himself"), possessives ("The mother's baby" versus "The baby's mother") and negative passive constructions ("The car is not being pulled by the truck"), they showed significant impairments in changing tense ("Every day he kisses his nanny, yesterday he -"; control group: 9/10, patients: 3/10), forming plurals of nonsense words and several other specific grammatical tasks. Gopnik concludes that they do not have problems with plurals of known words, since they have a separate lexikon entry for those as opposed to applying a morphological rule. In the case of nonsense words, they cannot use this strategy and hence show significantly lower success rates than the control group. She sees the deficit as a selective inability to generate (or apply) morphosyntactic rules such as those for tense, number and gender marking and postulates a "feature blindness" (Gopnik, 1990) of affected KE individuals.

A comparison of the symptoms of the KE family with Broca aphasics shows striking similarities in impairments of oral praxis (Alcock et al., 2000) and grammatical competence, for example in the production of regular and irregular past tense and tests of derivational and inflectional morphology (Watkins et al., 2002). The deficits in usage of morphological markers therefore seem to be independent of the age of onset, as aphasics usually acquire normal language competence, and only lose specific abilities as a consequence of a traumatic event such as a stroke, while affected members of the KE family exhibit the deficits from the beginning. In contrast to shared morphological impairments, KE individuals performed by far better than aphasics on tests of semantic, phonemic and written fluency in various modalities (Watkins et al., 2002). These results can be interpreted as a corroboration of Gopnik's original claim of a selective impairment of feature markers, as they show a dissociation between morphological abilities and other linguistic competence and – at least on average – a more specific impairment than in aphasia.

In response to Gopnik's initial analysis of the KE family and her postulation of a feature blindness as the underlying deficit, Vargha-Khadem and Passingham

(1990) and Fletcher (1990) raised concerns about the validity of this claim based on a very limited test battery with a strong focus on only one aspect of the patients' dysphasia. Fletcher argues that calling the impairment in tense and plural marking "feature *blindness*" would be too strong, since their competence to mark features grammatically is not completely lost – as suggested by the use of the word blind – and would consequently prefer the term feature-impaired. Vargha-Khadem and Passingham (1990) noted, that also in the domain of morphology and syntax, patients fail in tasks that do not involve feature marking and that therefore the impairments in grammatical processing cannot be explained by feature blindness alone.

In general, Vargha-Khadem and Passingham (1990), Fletcher (1990) and Vargha-Khadem and coworkers (1995) stress that the disorder includes impaired processing and expression of other areas of grammar, grossly defective articulation of speech sounds, and a severe extralinguistic orofacial dyspraxia. In addition, their IQ values were on average 18-19 points below unaffected members and thus were close to the threshold for classification of a subject as having an impairment that is specific to language (Tallal et al., 1989; Lewis, 1992). According to these researchers, this would contradict the idea that a grammar specific gene underlies the defects. In contrast, Hurst et al. (1990) claim that "hearing and intelligence of all affected members were within the normal range" (p. 354) and also Lai et al. (2001) later state that, although some members have slightly lower IQ, others do not, despite still severe language problems, and that "therefore, non-verbal deficits cannot be considered as characteristic of the disorder" (p. 519).

For linguistic testing of the KE family, Gopnik (1990), Gopnik and Crago (1991) and Vargha-Khadem et al. (1995) compared 13-15 affected family members to eight unaffected, which constitute an almost perfect control group as "they have the same dialect, the same social class and the same upbringing" (Gopnik & Crago, 1991, p. 15). While Gopnik (1990) and Gopnik and Crago (1991) claim to have identified specific grammatical areas affected in the dysphasic family members, Vargha-Khadem et al. (1995) report that only object naming is unimpaired. The syndrome would therefore constitute a diffuse "speech disorder", where it can be expected that grammar will be affected as well. The two studies thus came to very

different conclusions after testing the same set of subjects, and their (to a large extent contradictory) results are presented in table 2.1.

Gopnik (1990) reports that the affected subjects are considerably more impaired when it comes to applying a rule to nonwords, since for existing words they might use different strategies to circumvent their problem like a separate lexical entry for the plural form or the past tense of a verb. Further support for the existence of separate lexical entries as opposed to generating derived forms using grammatical rules comes from studies measuring processing times for grammatically simple and complex words (Kehayia, 1994; Kehayia, 1997). While for the control group it takes more time to process a grammatically complex word like walked or zashed than their simple counterparts walk and zash, there is no differences in processing times for the dysphasics tested, indicating the same process in analyzing the words, i.e. lexical retrieval. Gopnik (1997) postulates that this might be a general strategy of grammar-impaired patients and also apply to affected members of the KE family. In contrast, no differences between regular and irregular verbs could be observed in a test of tense production, where subjects have to change common regular and irregular verbs between present and past tense (Vargha-Khadem et al., 1995). This pattern cannot be explained by a rule deficit because irregular verbs should not be affected in this case. Another indication for this view comes from the fact that 41% of errors reported by Vargha-Khadem et al. (1995) are overregularizations, indicating that knowledge about rules for tense marking is at least in part present. Nevertheless, it is hard to evaluate, to what extent this is indeed application of a morphological rule as a part of language competence in terms of an "internalized, unconscious set of rules" (Gopnik & Crago, 1991, p. 18), or just a consequence of many years of speech therapy, where the individuals are being explicitly taught the rules of English tense and number marking. In this respect, the age and the time of therapy might be one of the factors explaining the discrepancy between Gopnik and Crago and the study by Vargha-Khadem and colleagues conducted several years later on the same subjects. In addition, Vargha-Khadem et al. (1995) speculate, that the larger sample of sentences in their study compared to the earlier ones (40 vs. 10 sentences) could account for the different outcomes.

Gopnik & Crago, 1991

Task	Example		control	affected	p-value
pointing tasks	discriminate s-marked plurals by pointing - simple commands	perception	5.33	5.33	ns
	discriminate s-marked plurals by pointing - complex commands		3.83	3.33	0.361
nonsense plurals		production	5.00	2.83	0.008
complex commands		perception	11.83	10.67	0.097
syntactic comprehension	*he washes him* vs. *he washes himself*	perception			
	reflexives		5.50	5.67	0.599
	gender pronouns		3.83	3.67	0.549
	passives		3.33	3.00	0.563
	possessives		5.00	4.83	0.340
grammaticality judgments of feature errors	The boy eats three cookie.	perception	27.50	17.70	0.000
	corrections of the errors	production	18.33	7.83	0.000
derivational morphology	*There is a lot of sun. It is very ____.*	production	7.17	3.00	0.003
grammaticality judgements; thematic relations		perception	10.17	9.83	0.604
	corrections	production	3.50	3.50	ns
tense marking	*Every day he walkes eight miles. Yesterday he ____*	production	9.17	3.83	0.001
listening comprehension	questions about a short story	perception	4.67	4.50	0.687
narrative tasks	tell a story based on pictures, full noun phrases are counted (as opposed to pronominal noun phrases)	production	55.17	91.20	0.000

Vargha-Khadem et al., 1995

Task	Example	control	affected	p-value
Tests of language				
Digit span	Repeat this list of numbers	10 ± 2.83	6.3 ± 2.4	0.005
Alphabet words	Repeat this word (each begins with a different letter)	38.75 ± 0.71	29.58 ± 4.66	<0.001
Repetition of words		37.33 ± 2.81	18 ± 5.92	<0.001
Repetition of nonwords		34.88 ± 5.38	16.38 ± 5.44	<0.001
Lexical decision	Is this a real english word?	54.57 ± 4.89	46.91 ± 6.95	0.022
Sentence repetition		12.25 ± 5.57	3.64 ± 5.01	0.003
Object naming		30.13 ± 2.8	26.33 ± 4.38	0.903
Picture vocabulary	Show me the picture for this word	85.13 ± 10.84	65.38 ± 11.37	0.054
Phoneme deletion	Say this nonword without the first sound, e.g. varg > arg.	22.14 ± 1.57	12.5 ± 5.62	<0.001
Phoneme addition	Say this nonword without the first sound, e.g. varg > arg.	21 ± 3.65	14.08 ± 5.98	0.013
Nonword reading		23 ± 9.76	9.08 ± 5.11	0.001
Nonword spelling	Write this nonword as if it were a real English word	19.86 ± 7.95	7.83 ± 7.3	0.004
Rhyme production	Tell me a word that rhymes with this word	20.86 ± 7.47	13 ± 5.73	0.023
Tests of grammar				
Reception of grammar		76.57 ± 3.74	71.1 ± 4.82	0.024
Tense production		37.43 ± 3.55	19.91 ± 5.24	<0.001
Production of morphological markers	words: This creature is smaller than this one, but this creature must be the _____.[smallest]	19.29 ± 0.76	14.17 ± 2.86	<0.001
	nonwords: This creature is ponner than this one, but this creature must be the _____.[ponnest]	16 ± 1.63	6.83 ± 2.76	<0.001
Jundgements of morphological markers	words: Which sentence is correct? *"Planes are faster than trains."* or *"Planes are fastest than trains."*	20.86 ± 2.19	14.2 ± 5.15	0.502
	nonwords: Which sentence is correct? *"Planes are donker than trains."* or *"Planes are donkest than trains."*	14.14 ± 5.01	9.22 ± 3.67	0.039

Table 2.1: Results from linguistic tests performed on unaffected and affected members of the KE family.

In general, it is hard to evaluate the validity of the claims made in both studies based on the presented tests, as they are considerably different and in many cases use different strategies to test for language deficits. Both studies have some

shortcomings or are too strong in their conclusions. Gopnik and Crago seem to neglect other aspects of language use and intelligence and claim that they are unaffected without proper testing (or retesting under the same conditions). In addition, the number of sample sentences could be higher, especially for the key test (tense production) where there is undoubtedly a defect, but mixing all kinds of tenses and aspects in one test and providing only 2-4 test words for each is most likely insufficient for a detailed analysis and any strong claims. Vargha-Khadem et al. (1995) show that affected members of the KE family perform significantly worse than the control group on a wide range of tasks, but fail to go into much detail concerning the grammatical deficits. Production of morphological markers (derivation and inflection) are tested as a whole and only divided into words vs. non-words. In addition, it is hard to follow, how they reach a statistically significant difference in the reception of grammar with very similar values and largely overlapping standard deviations (table 2.1, bottom). If this outcome was interpreted as an equal performance of controls and affected members, it would be in line with the test performed by Gopnik and Crago (1991) on syntactic comprehension and would present the strong defect in tense production as a more specific impairment.

Gopnik and Crago (1991) remark that in many other studies on inherited specific language impairment, the symptoms reported – although sometimes not linguistically well controlled – point into the same direction and are in congruence with the data they acquired from the KE family, such as problems with plurals, pronouns and tense (Samples & Lane, 1985) and an increased error rate on grammatical morphemes in dysphasics (Tomblin, personal communication to the authors, 1990). According to Gopnik and Crago (1990), this suggests a general pattern of impairments that are typical of language-specific deficits and – as a consequence – are therefore also not necessarily directly related to the underlying (somatic) cause.

Apart from linguistic abilities, Vargha-Khadem et al. (1995) also tested non-linguistic oral and facial movements and showed that the KE family's praxic deficits are not confined to articulation, but extend also to imitations of animal and machine noises and executions of non-vocal commands ("stick out your tongue, lick

your upper lip and smack your lip"). Although the authors admit that language deficits are an important aspect of the phenotype, deficits in the nonverbal domain are considered to be equally prominent.

In this study and related work it has been proposed that the language impairments are inevitable consequences of a deficit in motor control – especially in the "coordination of high-speed movements necessary for the production of intelligible speech" (Vargha-Khadem et al., 2005, p. 131) – and hence do not constitute the underlying symptom, but are just secondary effects. Undoubtedly, verbal dyspraxia is "the most overt feature of the disorder of the KE family" (MacDermot et al., 2005, p. 1074), and this might bias the interpretation of the language deficits. Marcus and Fisher (2003) collect and present evidence that contradicts the strong claim of Vargha-Khadem and others that grammatical problems are merely a consequence of an impairment in fine motor skills:

- Affected members of the KE family do not show impairments in easy oral tasks and the deficits in general are confined to the orofacial muscles, leaving e.g. limb movements unaffected (Alcock et al., 2000; Vargha-Khadem et al., 1998; Watkins et al., 2002).

- Complex orofacial movements are often impaired (Vargha-Khadem et al., 1998), but this does not significantly correlate with their speech deficits.

- The impairments are not limited to articulated language, also written language (as another example of language production) and even comprehension show deficits, which was also observed by Vargha-Khadem et al. (1995) and Watkins et al. (2002).

The fourth argument comes from brain imaging studies on affected KE individuals showing alterations in regions relevant for language processing. These data will be presented in more detail in the next section.

2.1.2 (Functional) neuroanatomical phenotype

2.1.2.1 Structural brain abnormalities

Normal scans using magnetic resonance tomography showed no differences in the more macroscopic brain structure between affected and unaffected members of the KE family (Vargha-Khadem et al., 1998; Watkins et al., 1999). Therefore, any structural abnormalities that might exist are too minor to be picked up by conventional methods (Vargha-Khadem et al., 2005). In order to detect more subtle differences in brain architecture, a more refined method of analysis, voxel-based morphometry, was used. Here, regional amounts of gray matter (as determined by a voxel by voxel analysis of the images) are compared over multiple scans of affected (n=6) and non-affected (n=7) subjects. A first analysis using this method (Vargha-

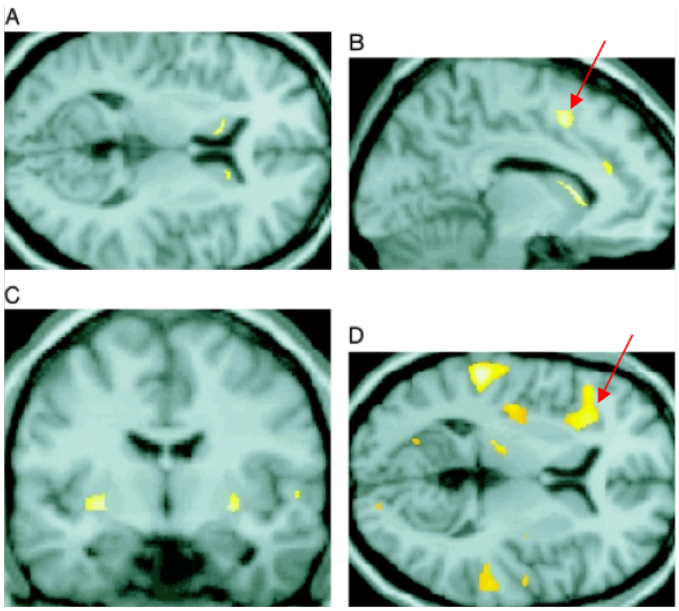

Figure 2.2: Morphometric analysis of affected KE family members. Colored areas exhibit changes in the amount of gray matter, including the caudate nucleus in both hemispheres (A), left medial frontal cortex (arrow) (B), putamen bilaterally (C) and left inferior frontal cortex (Broca's area, arrow) (modified from Watkins et al., 1999, Fig. 3).

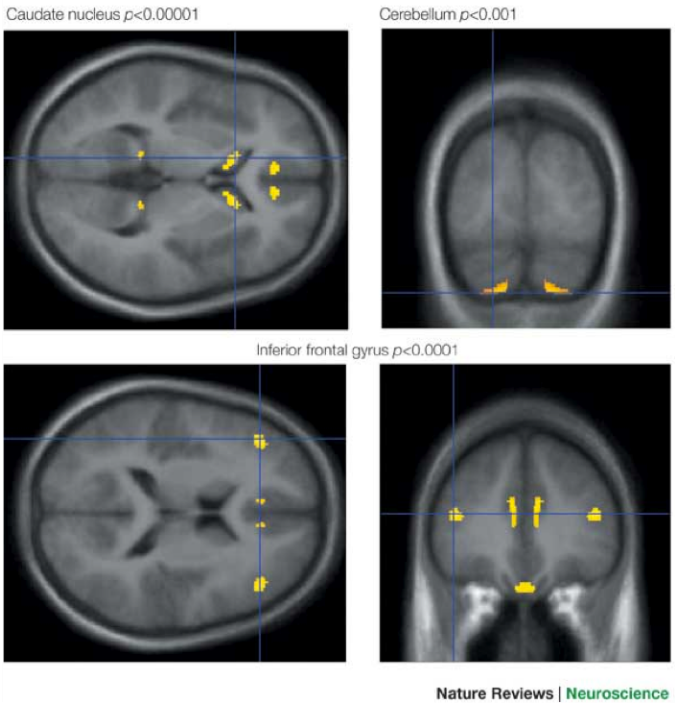

Figure 2.3: Voxel-based morphometry analysis of affected KE family members. Regions with significantly reduced gray matter are colored (from Vargha-Khadem et al., 2005, Fig. 2, based on Belton et al., 2003).

Khadem et al., 1998) showed abnormalities between the two groups in several areas: Some regions exhibit less gray matter (caudate nucleus, bilaterally, left medial and frontal cortex), while others showed an increase (putamen bilaterally, left inferior frontal cortex (BA45), left anterior insula, left and right planum temporale; see also Fig. 2.2).

Using an improved method Belton and coworkers (2003) detected lower levels of gray matter bilaterally in the inferior frontal gyrus (Broca's area), precentral gyrus (motor cortex), the temporal pole, the head of the caudate nucleus and the ventral cerebellum (Fig. 2.3), and higher levels of gray matter in the posterior portion of the superior temporal gyrus (Wernicke's area).

2.1.2.2 PET

Functional abnormalities in the brains of affected members of the KE family were first investigated by PET (cf. section 1.2.2). Four control individuals and two affected members of the KE family were presented with spoken real words or reversed words (Vargha-Khadem et al., 1998) and were asked to repeat them (in the case of a real word) or to say a previously specified word (in the case of a reversed word). Specific brain activation during this task was measured and regions of significant differences identified by comparing the activation patterns of the experimental and the control group. The two dysphasic subjects could produce all the target words – although less clearly than the control subjects – but showed several differences in activation patterns. Lack of activation compared to the control group was detected in the supplementary motor area (SMA), the subjacent cingulate cortex and the preSMA/cingulate cortex (Fig. 2.4, panel A), all in the left hemisphere only. A reduced degree of activation could be observed in the left sensorimotor face and mouth region. Regions of elevated activity comprise the left caudate nucleus and the left premotor cortex (Fig. 2.4, panel B), extending to BA44, and BA47/45, hence covering most of what is defined as Broca's area.

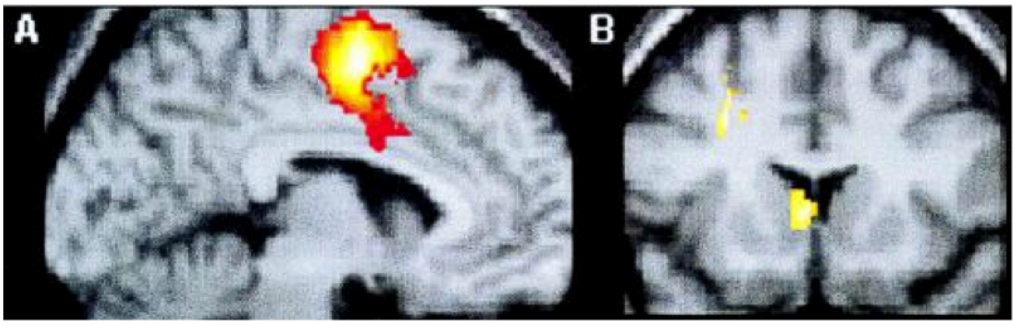

Figure 2.4: PET scan sections showing regions of decreased (A, (pre)supplementary motor area, cingulate cortex) and increased activity (B,head of the left caudate nucleus (yellow arrow) and left premotor cortex (red arrow)) in affected members of the KE family compared to control subjects (modified from Vargha-Khadem et al., 1998, Fig. 3).

2.1.2.3 fMRI

Liegeois and coworkers (2003) performed an fMRI analysis of five affected and five unaffected members of the KE family. They used both a covert and an overt verb production task in which the subjects were asked to generate a verb from an acoustically presented noun and either spell it out or not. In the covert verb production task, the control group showed the expected dominant activation in the left inferior frontal cortex, namely in Broca's area (Fig. 2.5, panel A, left). Strikingly, affected members of the KE family almost completely lacked activation in this area, but

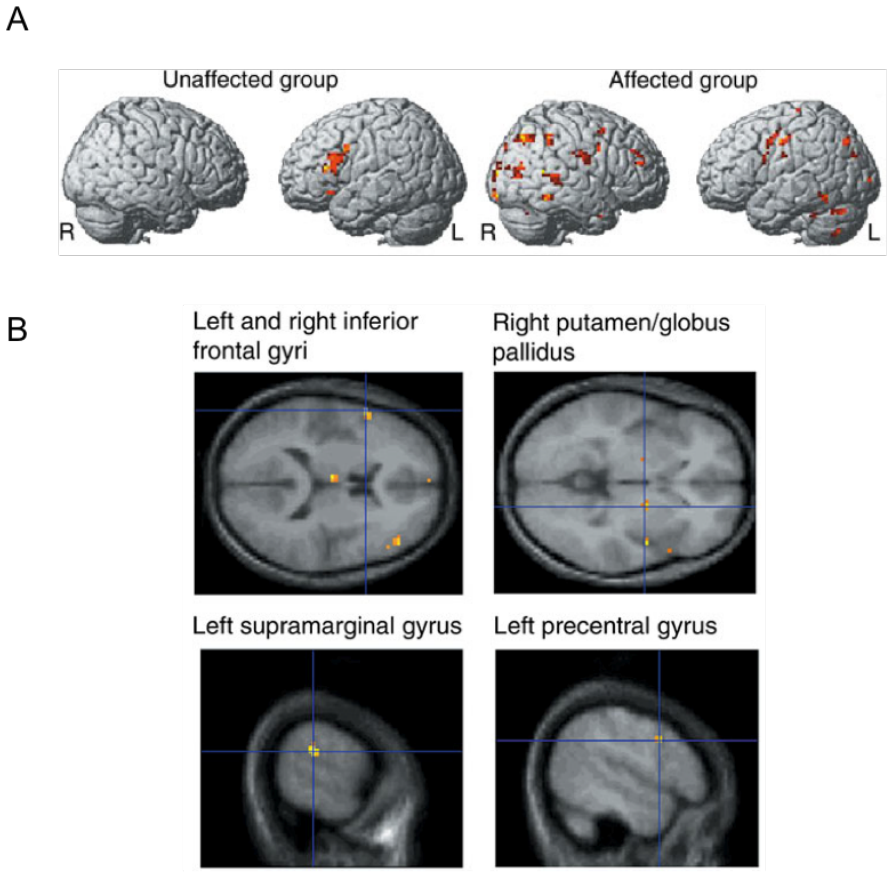

Figure 2.5: fMRI-based activation pattern elicited by a covert language task (A) and regions with reduced activity in affected family members (B) (modified from Liegois et al., 2003, Fig. 1 and 2).

instead exhibited diffuse activation in many more posterior parts of the left hemisphere (including Wernicke's area) and anterior, temporal and parietal regions in the right hemisphere (Fig. 2.5, panel A, right, and panel B). Interestingly, many of the regions with atypical activation were previously shown to have altered morphology, including the left inferior frontal gyrus (Broca's area) and the putamen/globus pallidus.

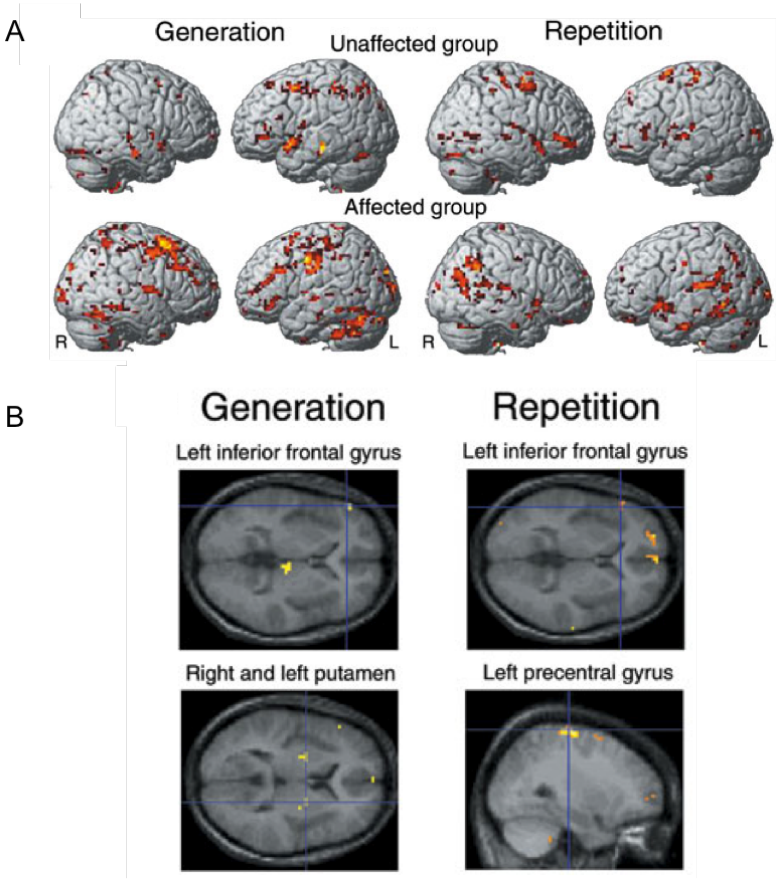

Figure 2.6: fMRI-based activation pattern elicited by an overt language task (A) and regions with reduced activity in affected family members (B) (modified from Liegois et al., 2003, Fig. 4).

To exclude that these changes were due to specific requirements of the covert production task, including semantic retrieval and producing utterances without spelling them out, the authors also performed overt tasks, namely on verb gener-

ation and word repetition. In contrast to the covert task, overt verb generation resulted in an activation of Broca's area, although this was significantly reduced compared to the control group, as was the activity in the putamen bilaterally (Fig. 2.6, left). In the word repetition task on the other hand, activation could be detected neither in the inferior frontal gyrus nor in the left precentral gyrus (Fig. 2.6, right).

2.1.3 Interpretation of the results

The characterization of the deficits of the KE family gave rise to the assumption that the defects should be bilateral, because otherwise one would assume – given the plasticity and adaptability of the developing brain – that in a unilateral defect the unaffected hemisphere could compensate for the deficits (cf. Watkins et al., 2002). In many patients with early acquired lesions in the left inferior frontal hemisphere, the corresponding region in the right hemisphere could at least in part compensate for that and showed overactivation compared to healthy controls. Compensatory mechanisms can also be seen in affected members of the KE family, as e.g. verb generation tasks lead to a diffuse activation of many other parts in both hemispheres, but not in the contralateral inferior frontal gyrus (Liegeois et al., 2003), arguing for a bilateral deficit also in this area.

Liegeois et al. (2003) report an overactivation in more posterior regions, e.g. Wernicke's area, as a compensatory mechanism for the lack of activity in Broca's area in the covert verb generation task. The authors suggest that this might reflect a different cognitive strategy to form the target word, namely activating more semantic memory circuits as opposed to grammatical processing and derivation. This can be interpreted as neurolinguistic support for Gopnik's original claim, that instead of using derivational and inflectional mechanisms, affected members of the KE family rather use different lexical entries for derived word forms and thus also access and process them in a more semantic or – in a simplified view – "Wernicke-based" way.

Brain region	Hemisphere	Structural abnormalities (Vargha-Khadem et al., 1998)	Structural abnormalities (Belton et al., 2003)	PET (Vargha-Khadem et al., 1998)	fMRI (Liegeois et al., 2003)
caudate nucleus	left	less gray matter	less gray matter	elevated signal	less activity
	right	less gray matter	less gray matter		less activity
putamen	left	more gray matter			less activity
	right	more gray matter			less activity
inferior frontal cortex (Broca)	left	more gray matter	less gray matter	elevated signal	less/no activity
	right		less gray matter		
posterior superior temporal gyrus (Wernicke)	left		more gray matter		more activity
	right		more gray matter		more activity
cerebellum	left		ventrally less gray matter		
	right		ventrally less gray matter		
precentral gyrus (motor cortex)	left		less gray matter	elevated signal	more activity
	right		less gray matter		
supplementary motor area (SMA)	left			reduced signal	
	right				

Table 2.2: Comparison of structural and functional alterations in members of the KE family suffering from a language disorder.

Although the results from the different studies present different brain regions like the inferior frontal gyrus and the caudate nucleus as hotspots of misregulation in the brains of affected members of the KE family, the nature of these abnormalities are contradictory or at least hard to accommodate in a unified account for the deficits observed. On the one hand, structural and functional abnormalities are not always correlated (table 2.2). Therefore, some aspects of an unusual activation pattern during language tasks could be seen as secondary effects of abnormalities elsewhere in the brain, either by compensation or – in the case of downstream regions – by lack of input from upstream processing centers in the brain. Even in regions where both structural and functional abnormalities have been detected, the relationship between them is unclear. A reduced density or volume of gray matter might correspond to lower activity in functional scans (simply because there are less neurons in this area that could consume oxygen) or higher activity as a means to compensate for the reduced volume and/or the lower number of neurons in this region (Liegeois et al., 2003; Vargha-Khadem et al., 1998). In some cases, however, different studies report either higher or lower amounts of gray matter for a certain area (e.g. Broca's area, Vargha-Khadem et al. (1998) vs. Belton et al. (2003)) or elevated or reduced activity (e.g. for Broca's area, Vargha-Khadem et al. (1998) vs. Liegeois et al. (2003)). For the studies using functional imaging techniques, this discrepancy might be a consequence of the different methods (PET vs. fMRI) or language tasks used, but for the evaluation of structural abnormalities, explanations for the divergent results are harder to find.

Liegeois et al. (2003) emphasize the apparent similarities in the impairments of affected family members with Broca aphasics and relate this to the underactivation in Broca's area that corresponds to a lesion in the aphasic patients.

Another particularly promising candidate for a region connected with the language impairments is the caudate nucleus, as Watkins et al. (2002) showed a correlation between the volume of the caudate nucleus (reduced by up to 20% compared to control) and the performance of affected family members in nonword repetition to test for oral practic abilities. In addition, acquired damage to subcortical areas like the putamen and the caudate nucleus can result in language deficits (Pickett et al., 1998), showing that also the morphological and functional abnormalities in these areas could contribute to the symptoms of the KE family (Liegeois et al., 2003).

Vargha-Khadem et al. (1998) mention that one possible account for the language deficits in the KE family would take the abnormalities in the motor cortex to be the source of the problem. The effects of these changes could then be mediated by subcortical structures, among others the caudate nucleus and the putamen. The authors, however, rather favor another possibility, namely that the underlying deficit is located in the striatum (containing the caudate nucleus and the putamen), which projects indirectly to the frontal cortex. Neuronal circuits involving the basal ganglia are very complex, so an unambiguous interpretation of the abnormalities is not yet possible. In addition, evidence from the other studies reported here revealed a correlation of morphological and functional alterations not only in the striatum, but also in cortical regions like Broca's area, and thus make it more likely that both areas have an underlying deficit and that it will not be possible to explain changes in activation patterns in either of them just as secondary effects of abnormalities in the other. In general, the different lines of neurolinguistic evidence from affected members of the KE family support a putative frontostriatal pathway that is involved in language processing (Liegeois et al., 2003; Pickett et al., 1998), but the question which of these areas (or if all of them) actually contribute to the language deficits in the patients still remains unanswered.

2.2 The discovery of FOXP2 and its molecular function

2.2.1 Identifying the underlying cause of the defects of the KE family

Since the first characterization of the aggregation of the disorder in the KE family, researchers have speculated that – given the simple Mendelian pattern of inheritance – the underlying cause should be found in a single genetic locus (Gopnik, 1990; Hurst et al., 1990; Vargha-Khadem et al., 1995). The pattern of inheritance (approximately half of the individuals affected, no sex bias) suggested a dominant autosomal mutation, i.e. a dominant alteration on one copy of one of the 22 human chromosomes that are not sex-specific (excluding X and Y chromosomes). Given the large number of individuals that could be tested, a linkage analysis (see section 1.3.1.3) with known markers could be performed (Fisher et al., 1998). Here, co-inheritance with genetic markers of known location is scored for members of all three generations of the KE family (cf. Fig. 2.7). Using this approach, the affected region could be narrowed down to a 5.6 cM (corresponding to approximately 5.6 million basepairs) interval on the long arm of chromosome 7.

This region contained several genes that could be responsible for the phenotype, and at that point it could not be ruled out that it was actually not a single gene, but a small deletion affecting several genes located in close proximity. The identification of an unrelated case (CS) with a similar clinical appearance and a known chromosomal rearrangement involving parts of the long arm of chromosome 7 helped to further narrow down the region (Lai et al., 2000; Lai et al., 2001). Lai et al. (2001) identified the breakpoint of this chromosomal rearrangement on chromosome 7 and found that it was inside a gene with a region similar to the DNA binding domain of the forkhead/winged-helix (FOX) family of transcription factors. According to the nomenclature for this gene family it was assigned the name FOXP2. Testing the KE family for mutations in this gene resulted in the identification of a single guanine residue that was changed to an adenine in all of

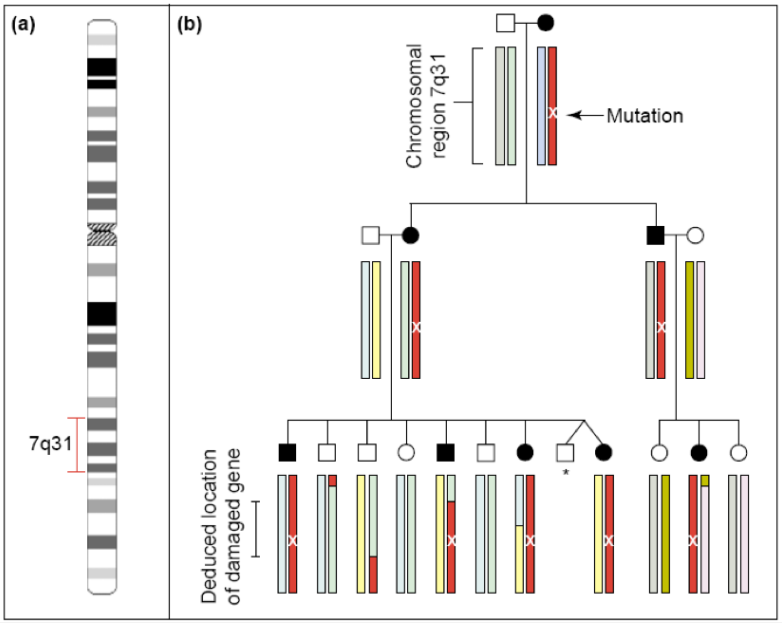

Figure 2.7: Locating the gene responsible for the impairments of the KE family using the frequency of co-inheritance with markers of known location. This approach allowed Fisher et al. (1998) to narrow down the region to a relatively short interval on the long arm of chromosome 7 (from Marcus & Fisher, 2003, Fig. 1).

the affected family members. A test of 364 other unrelated individuals with a similar ethnic background showed that all of them – like the unaffected members of the KE family – had the canonical guanine in this position. Therefore this change does not constitute a natural occurring polymorphism, i.e. a common variability in the genetic code without major functional implications, but likely constitutes the causative mutation in the KE patients. This is further corroborated by the fact that this guanine-to-adenine transition leads to a change in a highly conserved amino acid (histidine instead of arginine at position 553, R553H) in the DNA binding domain of the corresponding FOXP2 protein. This mutation is thus likely to interfere with the molecular function of the protein, as has been shown in vitro for the corresponding mutation in a closely related protein of the same family, FOXC1 (Saleem et al., 2003).

2.2.2 Additional evidence for a role of FOXP2 in language

The KE family did not remain the only example where a mutation in the FOXP2 gene was reported to result in a language deficit. One case is the aforementioned patient CS. CS suffers from symptoms very similar to the KE family with substantial impairments in expressive and receptive language competence and severe orofacial dyspraxia, while gross motor functions are intact and also the IQ is only mildly affected, presenting the verbal domain as specifically severely impaired (Lai et al., 2000). Lai and coworkers identified a chromosomal rearrangement between chromosomes 7 and 5 as the cause of his condition. The breakpoint on chromosome 7 is inside the FOXP2 gene, leading to a lost functionality of the gene.

MacDermot et al. (2005) specifically tested 49 probands with deficits similar to KE and CS for mutations in the FOXP2 gene. As a criterion, patients to be tested needed to have speech articulation problems, no mental retardation or hearing problems and normal karyotype (i.e. no gross abnormalities on the chromosomal level, like in the case of an additional copy of chromosome 21 in Down syndrome patients). Among some DNA sequence variations and polymorphisms, that should not have any major influence on the protein level, MacDermot and colleagues found three patients with mutations that would lead to a changed FOXP2 protein. In one case, this alteration is likely to have functional implications, since both the sibling and the mother of the proband who exhibit the same language problems harbor this (heterozygous) mutation, but not the unaffected father. In this case it is a cytosine-to-thymidine (C>T) transition that introduces a stop codon (i.e. a sequence that causes protein production to terminate there), namely the nonsense mutation R328X, and would thus lead to the production of a severely truncated protein that lacks many functional domains, among others also the FOX domain mutated in the KE family (all known mutations in the FOXP2 gene linked to language deficits are summarized in Figure 2.8). Given the more deleterious form of mutation in these patients, it is not surprising that their impairments were more severe than in the case of the KE family. They exhibited deficits that were most prominent in the domain of language production and comprehension, and

especially the children (at the age of 4 and 3, respectively) were unable to produce any utterances except single words and to repeat multisyllabic words. Testing using the Griffiths (1970) Mental Development Scales showed a delay in language skills of 1.5 to 2 years compared to the chronological age (MacDermot et al., 2005). After the KE family this study provides the first independent link between a point mutation in FOXP2 and language impairments.

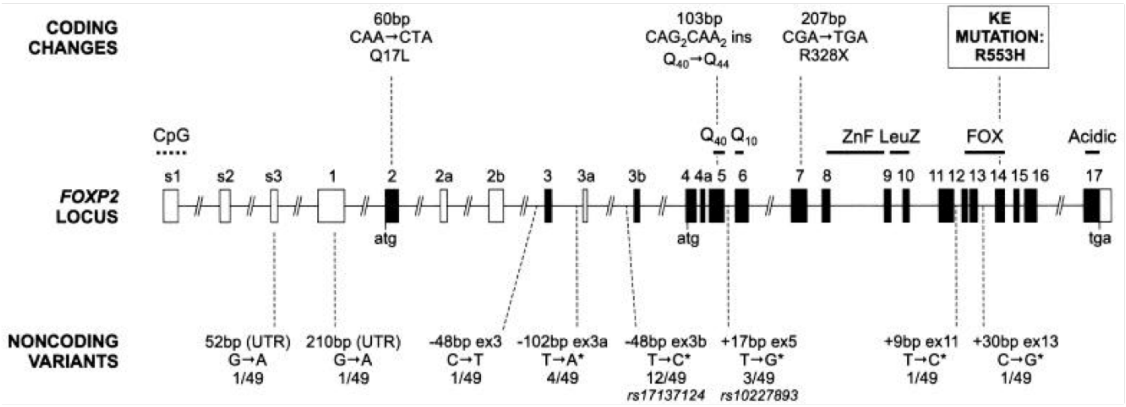

Figure 2.8: The human FOXP2 locus with the known alterations reported to lead to language impairments (from MacDermot et al., 2005, Fig. 1).

2.2.3 The molecular function of FOXP2

As mentioned above, FOXP2 belongs to the protein family of transcription factors containing a forkhead/winged-helix (FOX) domain. Transcription factors are proteins that – usually in a combinatorial way – mark a gene for active or repressed transcription. In the first case (Fig. 2-9A), their association with a specific DNA sequence close to a certain gene promotes recruitment of the transcription apparatus, the protein complex that synthesizes an RNA molecule from a DNA template, i.e. "transcribes" the gene. The RNA itself serves as the template for the production of the protein, which usually is the biologically active product of a gene. In the case of a repressive function of the transcription factor (Fig. 2.9B), its association with regulatory regions on the DNA next to the gene prevents the association of

the transcriptional machinery with the target gene and subsequently no RNA is made and the gene is inactive. Usually transcription factors act in a combinatorial manner, i.e. the sum of the activating and repressive effects of all the transcription factors bound to the regulatory region of a gene decides if (and to what extent) a gene is active or not.

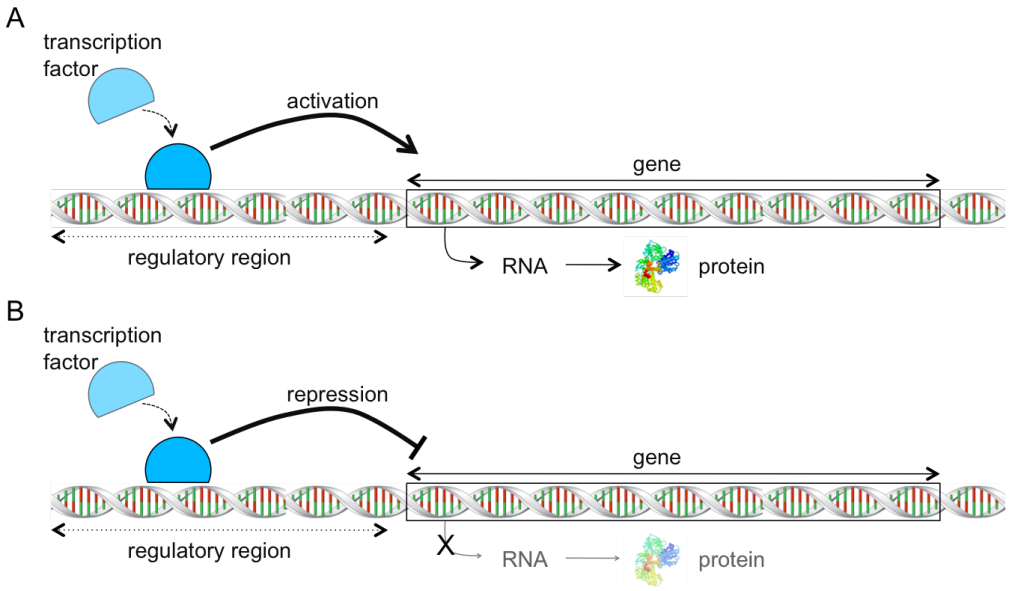

Figure 2.9: Functioning of a transcription factor. As an activator (A), binding of a transcription factor to a regulatory region in the genome can promote the expression of the target gene, as a repressor (B), it can silence the gene or reduce its expression.

The characteristic feature of the forkhead family of transcription factors is a sequence of 80-100 amino acids – the building blocks of every protein – that form a motif that binds to DNA, the Forkhead box (FOX) (cf. Carlsson & Mahlapuu, 2002).

The first member of this family was discovered in the fruitfly Drosophila melanogaster. A mutation in this gene resulted in unusual spiked-head structures in the fly embryo, which led to the name "forkhead". In general, mutations in FOX genes often result in developmental defects, affecting e.g. the eye, the immune system or the ovaries (cf. Carlsson & Mahlapuu, 2002; Marcus & Fisher, 2003).

In general, FOX genes seem to be involved in patterning of the embryo, and the number of FOX genes in a species correlates with the complexity of the body plan (Carlsson & Mahlapuu, 2002).

In the reported cases of language disorders involving FOXP2 one of the two copies of the gene (due to the existence of two copies – one maternal and one paternal – for each chromosome) was still intact, while the other one showed a mutation resulting in a complete loss of the protein or the production of a functionally inactive form. This indicates that a complete loss of FOXP2 might be embryonically lethal, and that wild-type amounts of the protein are necessary for normal development. This seems to be a common feature of FOX genes as, for example, control of FOXC1 protein levels was shown to be necessary for human eye development (Nishimura et al., 2001).

In summary, the forkhead family of transcription factors is typically involved in patterning of the embryo during development, i.e. in the realization of a body plan on the cellular level. Different members of this family seem to act in different tissues and developmental contexts, as mutations often lead to impairments in the development of a certain organ. Knowledge about the spatial and temporal presence and activity of FOXP2 in the body might therefore help to gain further insight into the link between FOXP2 and the neurological and neurolinguistic deficits associated with mutations in this gene.

2.2.4 FOXP2 expression

Since a reduction in functional FOXP2 levels leads to abnormalities in the brain, it can be expected that this gene is normally expressed at least in parts of the central nervous system. Lai et al. (2003) were the first to show that this is indeed the case. By *in situ* hybridization (detection of messenger RNA using labeled probes) on human fetal brain slices they could follow the onset and pattern of FOXP2 expression in the human brain, since the presence of messenger RNA of a gene is – with many caveats – a strong indication for the production of the protein corresponding to this RNA.

In general FOXP2 expression in the brain is not uniform, but seems to be highly regulated and shows a strong spatial and temporal specificity (Lai et al., 2003; Takahashi et al., 2003). In addition, also expression in a certain region of the brain is not homogenous, but almost exclusively found in neurons and often restricted to certain cell types (Ferland et al., 2003). Expression of FOXP2 in the human brain starts between 41 and 45 days of gestation, when *FOXP2* RNA can be detected at the midline of the hindbrain (Lai et al., 2003). The timing and localization of beginning FOXP2 expression is very similar to rodent brains, and this is also true for later developmental stages, indicating a high degree of conservation of FOXP2 expression regulation. By Carnegie stage (CS) 23, expression can be seen in confined areas of the medulla oblongata, parts of the cerebellar primordium, the medial region of hypothalamus and thalamus and the caudate nucleus (Fig. 2.10). As development progresses, the signal intensifies, especially in the thalamus, and appears in the developing inferior olivary nuclei of the medulla, but due to ethical limitations, the investigation was confined to early gestation (approximately the first 9 weeks post-fertilization).

Since FOXP2 expression cannot be followed over the entire human ontogenesis and given the similarities between human and rodent development as suggested by the same time of onset of FOXP2 expression and the similar expression pattern at early stages, an investigation of FOXP2 expression at later stages in rodent brains and the effect of FOXP2 mutations on the development of the central nervous system can provide useful information for the origin of the defect in humans.

Lai et al. (2003) observe the first expression in the mouse brain at embryonic day 11.5 (E11.5), when *FOXP2* mRNA can be detected at the area of the future medulla oblongata. Two days later, expression can also be seen in the cerebellar primordium, parts of the hypothalamus, some thalamic nuclei and the caudate nucleus, consistent with the data from humans at a comparable developmental stage (Fig. 2-10). The expression in these regions intensifies, and by the time of birth, *FOXP2* mRNA can also be detected in the inferior olives of the medulla.

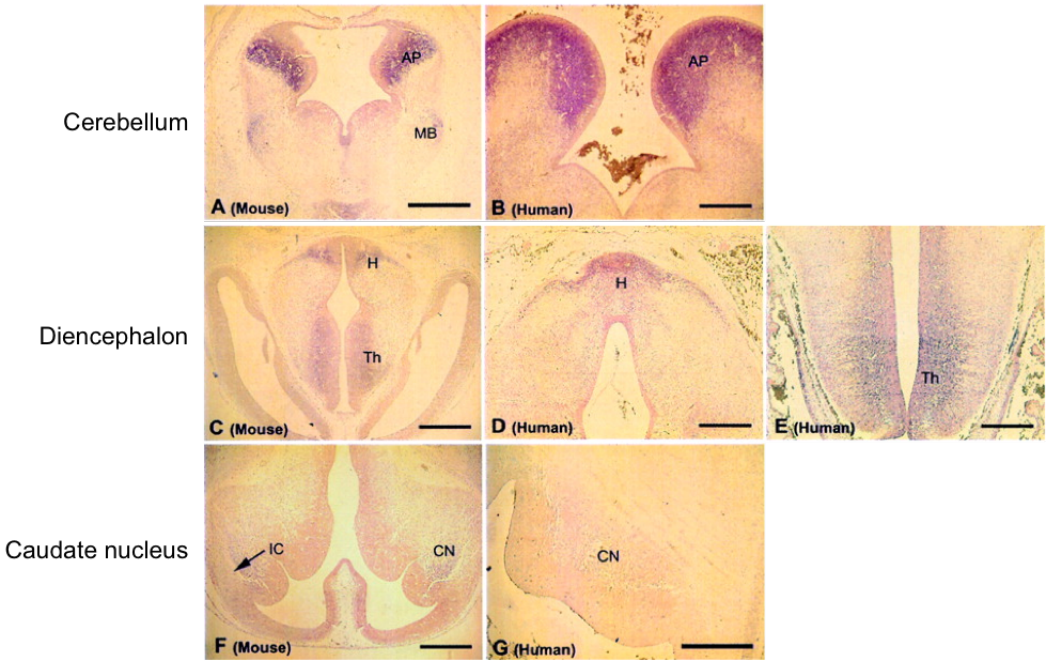

Figure 2.10: FOXP2 mRNA in the developing mouse and human brain. FOXP2 mRNA is detected by in situ hybridization at E13.5 in mice and a comparable embryonic stage in humans (CS23). AP = alar plate; MB = midbrain; H = hypothalamus; Th = Thalamus; CN = caudate nucleus, scale bars: 1mm for mouse, 0.5mm for human (modified from Lai et al., 2003, Fig. 1).

FOXP2 expression in the cerebellum is especially interesting, since it is mainly restricted to one cell type, namely Purkinje cells. Expression in these cells starts very early and persists, so that the question arises, whether FOXP2 might be involved in the development, differentiation or maintenance of Purkinje cells (Ferland et al., 2003).

Expression in the cortex can first be seen at E14.5, when mRNA is present in the lower regions of the cortical plate (Ferland et al., 2003; Lai et al., 2003). During development, this pattern is maintained and ultimately FOXP2 expression in the adult brain is restricted to layer 6 (Fig. 2.11), which is the innermost of the cortical cell layers and consists mainly of pyramidal cells that project

to the thalamus, another area rich in FOXP2 expressing nuclei (Ferland et al., 2003).

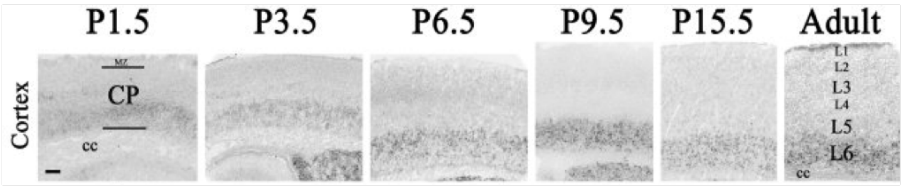

Figure 2.11: Postnatal FOXP2 mRNA expression in the mouse cortex. FOXP2 mRNA is detected by in situ hybridization at different postembryonic days (P) and as adults (where FOXP2 mRNA is restricted to the innermost cortical layer (L6)). CP = cortical plate; L = (cortical) layer (modified from Ferland et al., 2003, Fig. 2).

Ferland et al. (2003) – in addition to monitoring mRNA expression by in situ hybridization – also investigated the expression pattern of the protein and found it to overlap – as expected – to a large extent with the mRNA expression. In the ventricular and subventricular zone, however, where new neurons are generated through asymmetric division and differentiation of a neural stem cell and later on migrate to the various cortical layers, mRNA was present at low levels, but the protein could not be detected, indicating that production of the protein would only start once these neurons have migrated out of the ventricular zone into the cortical plate.

Takahashi et al. (2003) investigated FOXP2 expression in the developing and mature rat brain and focused their attention mainly on the striatum, since in this region FOXP2 turned out to be highly expressed and also the biggest anatomical differences in patients with FOXP2 mutations could be detected in this area. At E14, expression can be detected in a region that will give rise to the striatum. In postembryonic development, an interesting sublocalization pattern becomes visible in the striatum of the rat brain. FOXP2 expression can be seen as patches, and these patches colocalize with a marker for the striosomal compartment, a region in the striatum that is mainly present in the caudate nucleus and receives input mainly from the cortical area associated with the limbic system (located in the

medial frontal lobe), in contrast to the matrix compartments that receive input from the sensorimotor cortex.

Interestingly, although FOXP2 is very closely related to another family member of the forkhead transcription factors, FOXP1, the spatial and temporal regulation of expression is very different between these two, suggesting very different roles in the development of the mammalian brain, despite their very similar structure and probably common origin (Ferland et al., 2003; Takahashi et al., 2003). Another interesting aspect of FOXP2 expression, e.g. in the striatum, is the fact that – in contrast to other transcriptional regulators known to be involved in the development of these structures, which are only expressed there in the developing brain – FOXP2 expression in the striatum persists (although at reduced levels) into adulthood, suggesting a constitutive role in the function of these brain areas (Takahashi et al., 2003).

Comparing the brain regions showing changes in architecture in patients carrying a FOXP2 mutation and the expression data, it is evident that there is a large degree of overlap. Especially the caudate nucleus, which is both structurally and functionally affected e.g. in KE family members, and the cerebellum are both hot spots of FOXP2 expression in the developing brain and show alterations in fully developed brains of individuals with only one functional allele of FOXP2. Lai et al. (2003) suggest that the regions of FOXP2 expression in the developing brain are also the areas where an anatomical explanation for the language defects of affected individuals could be found. They note that many regions of FOXP2 expression have been implicated in motor control. The basal ganglia are thought to modulate the input from cortical motor areas, while the cerebellum – receiving input from the olivary nuclei – regulates motor coordination. FOXP2 expression in all of these areas makes it tempting to assume a role in the development of corticostriatal and olivocerebellar motor circuits. This role would be crucial for fine motor abilities, e.g. of the speech organs, and interference with the development of these pathways by reducing the amounts of functional FOXP2 could give rise to the orofacial dyspraxia observed in KE patients. This observation, however, is strictly focused on the motor control of speech and does not involve the underlying language competence that would then initiate a certain motor program to articulate

the grammatical structures generated in the brain. Takahashi et al. (2003) stress that the striatum is also involved in procedural memory. Based on the assumed localization of procedural memory-dependent mental grammar in the basal ganglia (Ullman et al., 1997; Ullman, 2001), the authors suggest that their results could point at a role for FOXP2 in forming the neural basis for information processing required for speech and language.

Expression of FOXP2 is not confined to brain regions. It was also shown to be present in the developing lung, heart and gut of the embryo (Shu et al., 2001) and for example has been shown to regulate lung and esophagus development in the mouse (Shu et al., 2007). The fact that one gene has several independent functions during development is not uncommon, and one transcription factor can regulate very diverse processes in different contexts and at different developmental stages (Marcus & Fisher, 2003). In the case of FOXP2, there seem to be different sensitivities to reduced level or functionality of the protein. While a mutation in both copies of FOXP2 (the maternal and the paternal one) leads to severe developmental defects and lethality probably due to malfunction of the respiratory system (Shu et al., 2007), the loss of one functional copy of the gene (as in the case of the KE family and the other reported cases of a language disorder associated with FOXP2 mutation) does not result in obvious problems in the respiratory system or other organs (cf. Marcus & Fisher, 2003). Thus, a reduced amount of functional FOXP2 is still enough to fulfill its function in other organs, but not in the brain (with so called haplo-insufficiency at least at a critical period during embryogenesis, Lai et al., 2001), possibly pointing at a highly regulated role in controlling development of specific brain regions.

2.2.5 The targets of FOXP2

As a transcription factor, FOXP2 contributes to the expression control of a number of target genes. Therefore, it is very likely that the role of FOXP2 in the development of the brain is not by directly affecting e.g. the shape or function of the cell by interaction with other cellular components, but rather by switching target genes on or off, which themselves are the effectors. Thereby, FOXP2 could be at the top

of a regulatory network that guides the development and functioning of motor and language related brain regions. This could provide an explanation, why mutations in the FOXP2 gene could only be found in a small minority (2% as suggested by MacDermot et al. (2005)) of patients with an inherited speech and language disorder with comparable symptoms. More incidents could then be caused by mutations in other components of this network, which are located downstream of FOXP2 and would lead to a similar phenotypic outcome (Fisher & Scharff, 2009). On the other hand this raises the possibility that these downstream factors regulated by FOXP2 could be even better – because more direct and potentially more specific – candidates for "language genes".

In 2007, two studies (Spiteri et al., 2007; Vernes et al., 2007) were published reporting the identification of FOXP2 target genes. Spiteri et al. (2007) performed chromatin immunoprecipitation (ChIP) to identify DNA sequences bound by FOXP2. In this method, FOXP2 is isolated from homogenized tissue using a highly specific antibody. Subsequently, short stretches of DNA that are still bound by FOXP2 are identified and mapped to the genome. Genes that are adjacent to or overlapping with a DNA sequence often found in association with FOXP2 are potential candidates for transcriptional regulation by FOXP2. Mere correlation of FOXP2 binding and genomic position of a gene is of course not enough to prove that this gene is indeed a target of the transcription factor. In addition, functional assays are necessary to show that absence or presence of the transcription factor has an effect on the expression of these candidate genes.

Given the diverse functions FOXP2 has during development in different tissues, it is very likely that also the set of genes that are regulated by it will not be the same in all of these contexts. Therefore, it is crucial to focus the analysis on a certain tissue and a defined developmental stage. Spiteri et al. (2007) performed their experiments at the time of high FOXP2 expression in two different tissues that show high FOXP2 levels and are potentially functionally relevant for the language deficits, namely the basal ganglia and the inferior frontal cortex (containing Broca's area). To obtain more information on tissue specific versus more global targets, the authors also determined potential FOXP2 targets in the lung, another tissue with high FOXP2 expression during development. The number of target genes that are

shared between different tissues or specific to one of the three data sets are shown in Figure 2.12.

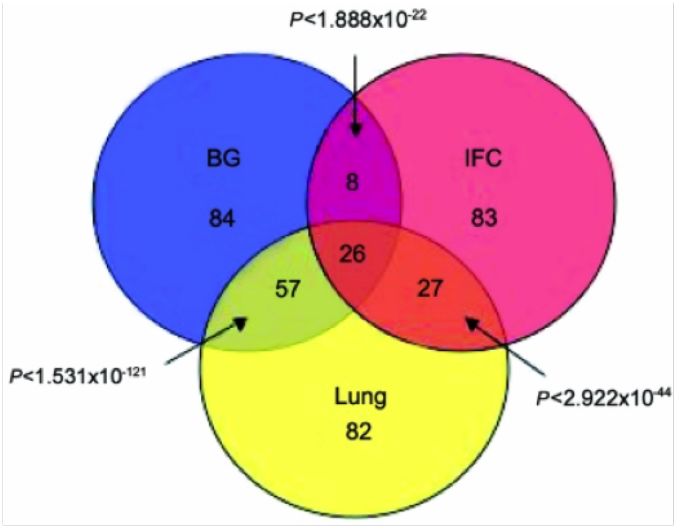

Figure 2.12: FOXP2 targets identified by Spiteri et al. (2007) in the human basal ganglia (BG), inferior frontal cortex (IFC) and lung using chromatin immunoprecipitation followed by microarray analysis. The number of significantly enriched targets and the overlap between these data sets are shown (from Spiteri et al., 2007, Fig. 3).

Interestingly, some of the eight nervous system specific genes (i.e. found in basal ganglia and the inferior frontal cortex, but not in lung ChIP) were already known to be involved in tissue patterning during development, like FGF8, a key effector of mammalian cortex patterning (Fukuchi-Shimogori & Grove, 2001), and two members of the homeobox family of transcription factors, which are known to be involved in patterning of the nervous system (Bel-Vialar et al., 2002; Prince et al., 1998).

Spiteri et al. (2007) went on to confirm their candidates as target genes of FOXP2 by testing the effect of FOXP2 overexpression (i.e. an increase in FOXP2 produced compared to a normal situation) on transcription levels of these genes. RNA expression levels of 19 genes found in the FOXP2 ChIP were compared between a neuronal cell line with or without artificially elevated levels of FOXP2.

While some genes showed a marked increase in RNA levels (Fig. 2.13, top), RNA levels of most of the candidates tested were reduced in the presence of high FOXP2 levels, indicating that although FOXP2 can act both as an activator and repressor of transcription, the repressive function is the more common one. For approximately 25% of the randomly tested candidates, RNA levels could be influenced by artificially changing FOXP2 abundance to an extent that reached statistical significance, which according to the authors is a typical value for positive functional validation of ChIP targets.

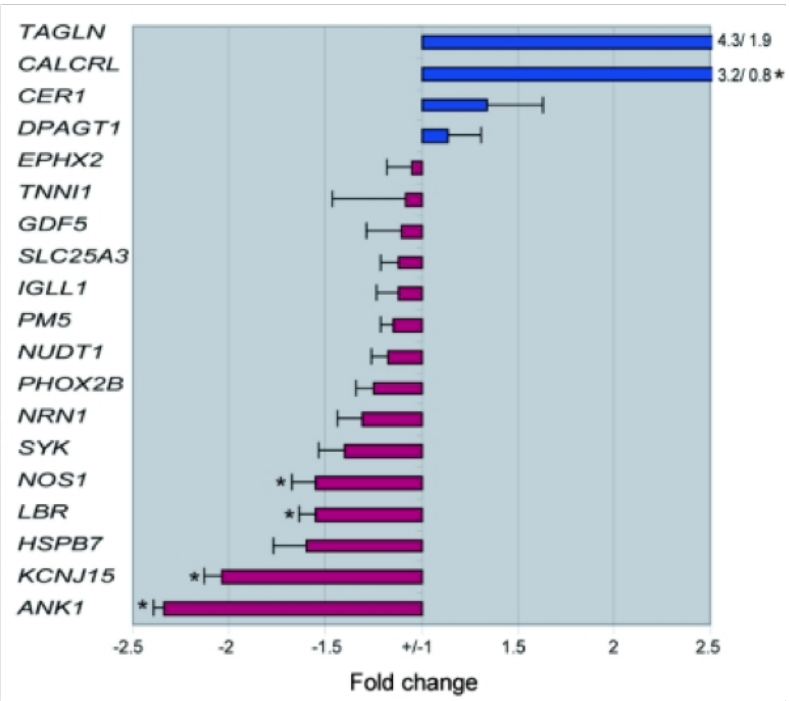

Figure 2.13: Changes in RNA levels of FOXP2 targets upon overexpression of FOXP2. Most of the genes tested show reduced expression in the presence of higher levels of FOXP2 arguing for a repressive function of FOXP2 in most contexts. Asterisks indicate statistically significant changes as determined by StudentÕs t-test (modified from Spiteri et al., 2007, Fig. 5).

In contrast to Spiteri et al. (2007), Vernes et al. (2007) performed FOXP2 ChIP followed by identification of bound DNA regions using a microarray on a human neuronal cell line. A comparison of the target genes between the two studies

showed a high number of common targets, which was surprising given the different input (cell culture versus isolated tissue) and the different antibodies used. Nevertheless, there are also many genes that seem to be regulated in a tissue-specific manner, since they were either identified in only one of the two studies or FOXP2 was shown to have an opposite effect on their expression in different tissues or experimental setup.

Following the initial identification of FOXP2 targets *in vivo*, Vernes et al. (2008) used a refined protocol, which allowed them to identify additional genomic regions bound by FOXP2 in a neuronal cell line. Here, the authors focused on one new candidate, CNTNAP2 (contactin-associated protein 2), which was particularly interesting because it had already been implicated in disorders involving language impairments, like autistic-spectrum disorder, Tourette's syndrome, cortical dysplasia associated with language regression and autistic characteristics (cf. Vernes et al., 2008). It also has a putative function in human cortical development and is expressed in language-related brain areas (Abrahams et al., 2007).

Following confirmation of FOXP2 binding to a potential promoter region in the CNTNAP2 gene using various methods, Vernes et al. (2008) investigated the effect of increased FOXP2 protein levels on *CNTNAP2* RNA and observed that also in this case, FOXP2 overexpression leads to a reduction in RNA levels compared to control cells. In concordance with its role as a transcriptional repressor, FOXP2 and CNTNAP2 expression are to a large extent mutually exclusive, which is especially apparent in the cortical plate, where CNTNAP2 can be detected specifically in those cell layers that do not express FOXP2 (Fig. 2.14).

To test if CNTNAP2 is associated with language impairments, Vernes et al. (2008) conducted family-based association studies, where families with cases of SLI and control families were tested for naturally occurring sequence variations, so called single nucleotide polymorphisms (SNPs). These results were then tested for a significant association with scores on a test for nonsense-word repetition. Nine SNPs could be identified that appeared in 11 combinations ("haplotypes") in the subjects tested. Strikingly, for the most common haplotype performance at the task also showed a correlation with the copy number of this haplotype in the genome (0 (none), 1 (plus a second CNTNAP2 allele of a different haplotype), or

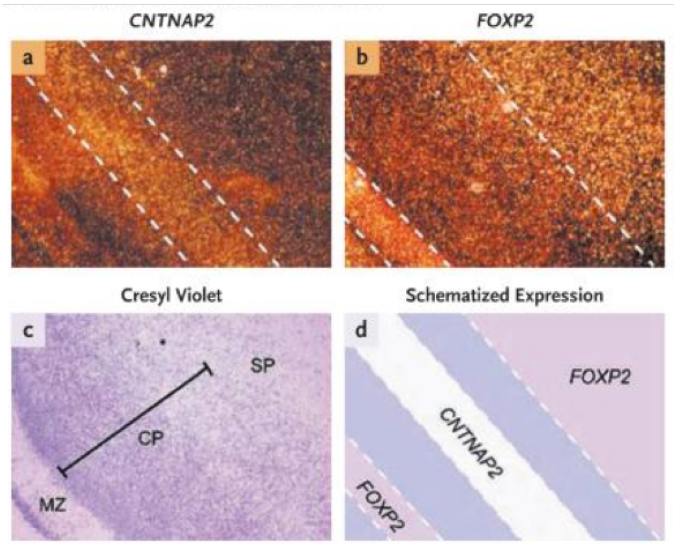

Figure 2.14: Complementary expression pattern of CNTNAP2 and its putative transcriptional regulator FOXP2 in human fetal brain. Detection of mRNA by in situ hybridization leads to a model of mutually exclusive expression (d). CP = cortical plate; SP = subplate; MZ = molecular zone (modified from Vernes et al., 2008, Fig. 2).

2 (both copies of the CNTNAP2 gene are of this haplotype)). The subjects for this study were selected for not being diagnosed with autism, in order to separate the language-specific deficits from secondary effects of a more general cognitive impairment. The authors argue that altered CNTNAP2 regulation could be a common mechanism underlying both SLI and autism, but with different molecular and genetic characteristics.

In a more recent study, Vernes et al. (2011) used again FOXP2 ChIP to identify potential targets, in this case in the mouse brain at embryonic day 16, a period of high FOXP2 expression (see section 2.2.4). Here, the authors did not focus on single candidates, but rather investigated if FOXP2 can be seen as regulating a specific genetic network. To do this, they performed bioinformatic analyses on the target genes and – from previous findings on the function of these genes – identified functional categories that are common among FOXP2 targets. Many

of these categories can be subsumed under the process of neurite outgrowth, i.e. the formation, specification and guidance of axons and dendrites in the developing brain. In the case of the network of genes regulating axon guidance, a surprisingly large fraction is directly or indirectly regulated by FOXP2. The authors could also show, that a mutation in FOXP2 that interferes with its normal function (much like in the case of the mutation in the KE family) leads to shorter neurites in murine basal ganglia (Fig. 2.15). This result is a strong indication that FOXP2 is involved in regulating specific aspects of neuronal development that are intricately linked to higher-order brain functions, as intact pathfinding of axons and dendrites constitutes a prerequisite for correct connectivity of neurons in different brain regions.

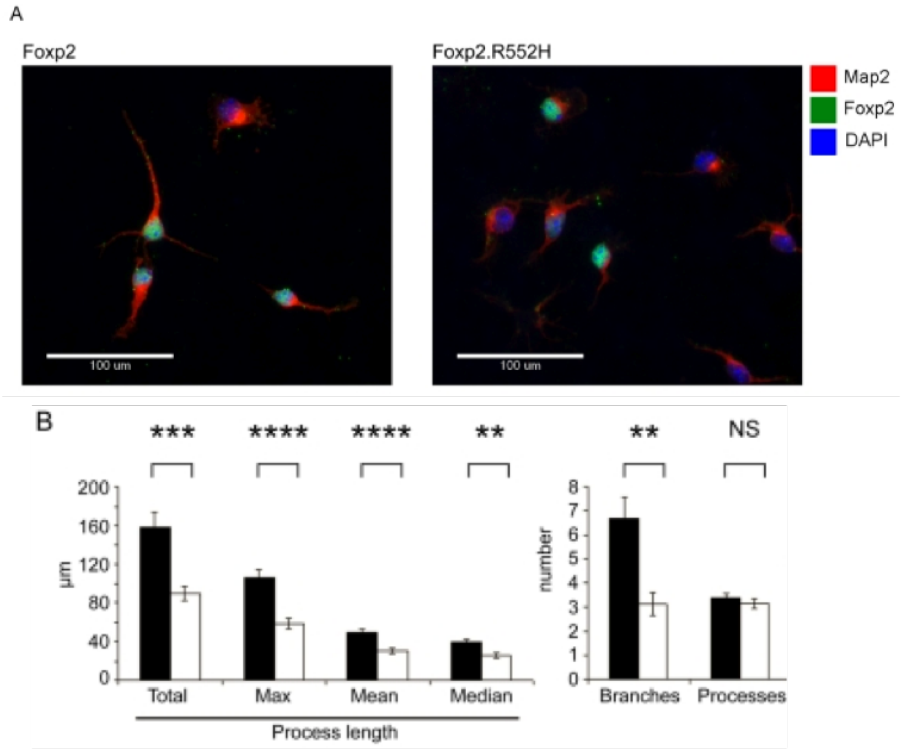

Figure 2.15: Mutation of FOXP2 leads to defects in neurite outgrowth in primary neurons. The length of the processes and the number of the branches is significantly reduced in a KE-like mutation of FOXP2 (modified from Vernes et al., 2011, Fig. 6).

In summary, the identification of target genes of FOXP2 is an important step in elucidating the mechanisms linking FOXP2 mutations with the observed deficits, but it is only the starting point. Especially CNTNAP2 is a promising candidate for mediating some aspects of the defect, but many other potential effector genes are yet to be characterized. Generating cell type-specific profiles of transcriptional targets and narrowing down the regulatory interactions between FOXP2 and its targets to individual types of neurons could contribute to a better understanding of the role of FOXP2 in tissue-specific networks (Fisher & Scharff, 2009; Scharff & Petri, 2011).

2.3 FOXP2 and evolution

Among the many criteria that are used to define us as humans, the ability to use a highly complex verbal communication system is the most widely used. Although other species have developed ways to communicate with their conspecifics by means of vocalizations, there are important differences between these and human language.

According to Di Sciullo and colleagues (2010), one important similarity between the human and other communication systems is the existence of an arbitrary association between sound and meaning, that is functionally referential in the sense that it is intended to trigger a specific action. On the other hand, this repertoire covers only a very narrow range of actually present objects and events. Even in songbirds and whales, who have a large repertoire of sounds and are also able to combine them in an iterative manner, similar to human language, there are important differences, in that this "combinatorial facility is independent of their conceptual system" (Di Sciullo et al., 2010, p. 7). This statement illustrates the fact that the combination of sounds does not lead to a more complex message, but has the same meaning as an individual sound (as far as this can be tested).

In the identification and characterization of a genetic basis for this specifically human endowment, the origin of a putative "language gene" and its presence or ab-

sence in other species becomes a crucial question. If this genetic feature is the basis for a uniquely human trait (or the human implementation of this trait), then it can be expected that there are marked differences in either the presence or the functionality of this genetic feature between talking humans and other species. This change is probably not affecting the anatomy of speech organs, but rather acts on the neurological level (Enard, 2011). Here, it could be an improvement in the neuronal networks coordinating fine motor movements of facial muscles or in higher order brain circuits that select the appropriate item from a mental lexicon and adapt and serialize them according to grammatical rules. The evidence pointing at FOXP2 as a potential "language gene" has drawn a lot of attention to its evolution and interspecies differences. In the following, I will present current theories concerning the origin and human-specific evolution of FOXP2 and highlight evidence implicating FOXP2 in the communicative abilities of other species.

2.3.1 FOXP2 in human evolution

Throughout millions of years of hominid evolution, brain size and complexity have expanded continuously. In the course of this increase in size, also the relative proportions of different brain regions have changed (Vallender et al., 2008). Notably the prefrontal cortex, an area crucial for social behavior in general and language competence in particular, has increased disproportionately (Semendeferi et al., 2002).

Human language is generally thought to have evolved following the principles of natural selection, i.e. an increase in communicative abilities must have had a more or less immediate advantage either for the group as a whole or the individual speaker (Bickerton, 2007; Brown, 2011). Following the Darwinian principles of evolution by natural selection, a newly acquired, advantageous feature (e.g. a mutation) would need tens of thousands of years to spread to the entire population and substitute the previous, slightly less beneficial haplotype (cf. Krause et al., 2007). Mutations in the genome occur at a certain frequency, and even between very closely related species like humans and chimpanzees this results in at least one amino acid difference between most homologous proteins, although this difference

Figure 2.16: Phylogenetic tree of vertebrate FOXP2 genes. Ticks indicate mutations leading to amino acid changes in the protein, the bars on the right depict the ratio of amino acid changes to the length of the terminal branch (as determined by synonymous base substitutions, i.e. not leading to changes in the protein). Asterisks indicate species with a (potential) ability for vocal learning (modified from Enard, 2011, Fig. 1).

does not necessarily have any functional implications (Vallender et al., 2008). In general, genes can have very different speeds of evolution, i.e. rates at which mutations are incorporated and lead to changes in the corresponding protein. High similarity of a gene even between not closely related species usually indicates a

high degree of functional conservation and an important function across species (Scharff & Petri, 2011). FOXP2 is among the 5% most highly conserved genes, but phylogenetic analysis revealed recent mutations in the human lineage that led to a difference in two amino acids compared to chimpanzees and three amino acids compared to mouse (Enard et al., 2002). Sequence analysis of the FOXP2 gene in different species and comparisons with phylogeny led to the conclusion that there was an evolutionary sweep that happened recently and ended 100.000 to 200.000 years ago, leading to an accelerated evolution of the FOXP2 gene in humans compared to other species (Fig. 2.16) and suggesting positive selection of these changes, potentially in order to adapt to a new function (Enard, 2011).

The two amino acid substitutions specific to the human lineage (T303N, N325S) are not located in any of the known functional domains (unlike the KE mutation that lies in the DNA binding region), so it is unclear whether these have any functional relevance. To test this, Enard and coworkers (2009) introduced a humanized version of FOXP2 into mice ($Foxp2^{hum/hum}$) and tested them for any behavioral, anatomical or molecular differences compared to mice expressing wild-type murine FOXP2 ($Foxp2^{wt/wt}$) and mice with only one functional copy of FOXP2 ($Foxp2^{wt/ko}$). Interestingly, while no differences could be detected in other parts of the body, the humanized version of FOXP2 exhibited the opposite effect to the loss of one allele ($Foxp2^{wt/ko}$) in a number of tests, e.g. for neurotransmitter levels, dendrite length of neurons in the striatum (Fig. 2.17) and their activity and synaptic plasticity, the cellular correlate of learning and memory. In a more detailed analysis of $Foxp2^{hum/hum}$ mice, Reimers-Kipping and colleagues (2011) noticed that the increase in dendrite length upon introduction of the humanized FOXP2 was only present in brain regions and cortical layers expressing FOXP2 and also among those not in all of them. Cerebellar cells did not show any differences depending on which FOXP2 version was expressed, so that the effect of humanized FOXP2 seems to be specific to the cortico-basal ganglia circuit (cf. Enard, 2011).

The fact, that the humanized version of FOXP2 in general had the opposite effect to a loss of one functional allele suggests that it is more active than murine Foxp2. Interestingly, this effect is restricted to the brain, more precisely to some of the brain areas expressing FOXP2, providing strong evidence that the subtle

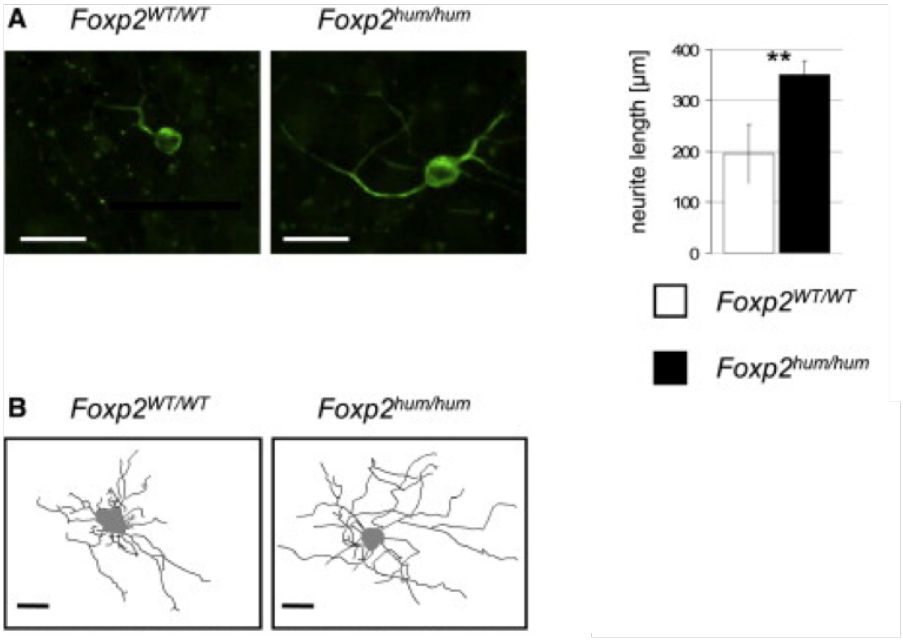

Figure 2.17: A human version of FOXP2 introduced into mice leads to an increase in neurite length. A: primary striatal neurons in culture, B: Representative drawings of medium spiny neurons of the two genotypes (modified from Enard et al., 2009, Fig. 4).

changes between human and mouse FOXP2 indeed have a functional relevance that is specific to its function in the brain.

As mentioned above, the two amino acid substitutions specific to human FOXP2 do not lie in any domain of known function, so the question arises, what the functional differences are that could explain the different effects of the human form in the mouse. One of the two mutations that have occurred in the human lineage creates a potential regulatory site on the protein that could lead to a differential regulation of the activity or stability of the protein (Cooper, 2006; Enard et al., 2002). Since FOXP2's function as a transcription factor is the regulation of the expression of target genes, Konopka et al. (2009) investigated if the human and the chimp protein (representing the ancestral form of FOXP2) would differ in their ability to regulate target genes in a human cell line. The authors indeed found 61 genes that were upregulated and 55 genes that were downregulated in

the presence of human FOXP2 vs. chimp FOXP2. Although the exact mechanism by which the two mutations affect the selection of target genes or the effect of FOXP2 binding to their promoter region still remains elusive, these data indicate that the human specific changes indeed led to functional changes in the protein and altered downstream effects through a different regulation of target genes, raising new questions about human specific pathways regulated by FOXP2 (cf. Dominguez & Rakic, 2009). More specific investigations on the effect in vivo – or at least in cells that are more relevant to the phenotype – will be needed to really evaluate if the surprisingly extensive differences reported by Konopka et al. (2009) indeed resemble a profound functional difference of FOXP2 in human and chimp brains (Enard, 2011).

Recent evidence from paleogenetic studies challenges the existing scenario of the appearance of the human-specific mutations 1-200 000 years ago. Krause et al. (2007) isolated DNA from two Neanderthal individuals found in Spain and sequenced the FOXP2 locus. Since the lineages of Neanderthals and modern humans are thought to have split at least 300 000 years ago (Weaver et al., 2008), it came as a surprise when the experiments showed that the same two mutations (previously assumed to be specific to modern humans) were present in Neanderthals. Since it is very unlikely that these changes occurred independently from each other and traditionally it had been assumed that Homo sapiens and Homo neanderthalensis did not interbreed, the authors propose that the mutations occurred in the common ancestor of H. sapiens and H. neanderthalensis and thus the current dating has to be revised. In addition, it is an additional piece of evidence in the longstanding debate on the kind of communication system Neanderthals were using (Trinkaus, 2007). Given the complex social behavior archeological findings suggest Neanderthals to have had (cf. Trinkaus, 2007), some sort of elaborate communication system must have been present to achieve this, and the data on the FOXP2 gene could suggest that this communication system might have been closer to human language than previously thought.

Although the findings of Krause et al. (2007) can lead to new and exciting scenarios about the emergence of human language ability, there are several caveats that have to be considered when drawing conclusions from the data presented. On

a purely conceptual level, Coop et al. (2008) raise concerns about the assumptions of a selection of the beneficial haplotype more than 300 000 years ago. From variation data in modern humans the authors tried to predict the time of the most recent common ancestor based on the variability at genomic positions that can be supposed to have no influence on protein function and thereby should not be under any positive or negative selection, but change purely stochastically at a certain frequency (a method known as phylogenetic dating). This computational approach suggests a common ancestral haplotype approximately 42 000 years ago, which would correspond to the time of the fixation of a beneficial genetic change in the whole population – and a starting point for new variability in this locus. Although this method is associated with considerable uncertainty, the difference to the time that has to be assumed for a common ancestor of H. sapiens and H. neanderthalensis is impressive. Following this argument, the assumption made by Krause et al. (2007) "cannot account readily for patterns of variation in modern humans" (Coop et al., 2008, p. 1257) or would – in an unlikely scenario – imply a dramatically reduced mutation rate at this locus. This argument, however, is based on genome-wide frequencies in variation and do not take into account the more "conservative" microenvironment of this specific change, namely a highly conserved gene in which sequence changes can be expected to be less frequent.

Moreover, Coop et al. (2008) also raise other conceptual and technical concerns. On the one hand, a low, but non-zero admixing between Neanderthals and modern humans is a realistic scenario for the appearance of the H. sapiens version of FOXP2 in the Neanderthal population. On the other hand, the authors state that with the control experiments performed by Krause et al. (2007), a contamination with modern human DNA – a common problem in the analysis of DNA from ancient samples – cannot be excluded. Fisher and Scharff (2009) also caution against too strong conclusions based on these results, as "the status of a single gene in ancient DNA is insufficient to resolve long-standing debates over linguistic capacities of our extinct ancestors" (p 173).

2.3.2 FOXP2 in other species

FOXP2 as a highly conserved gene that is expressed in a variety of tissues likely serves a plethora of crucial functions both in humans and in other species. In this context, the focus is on its role in the brain and – more specifically – the mechanisms by which it enables humans to speak. Given the high degree of conservation of expression patterns across species and the comparatively subtle changes of the protein, the question arises, if FOXP2 plays a comparable role in the vocalizations of other species.

2.3.2.1 Rodents

As one of the best studied organisms, for which the similarity in expression pattern and – despite subtle differences (Enard et al., 2009; Reimers-Kipping et al., 2011) – function in the brain has been established, research on mice has also focused on a potential effect of FOXP2 mutations on vocalizations.

The vocal repertoire of rodents consists of frequency modulated sonic (20-20 000 Hz) and ultrasonic (>20kHz) sounds and clicks. While the first category is produced by vibration of vocal chords, ultrasonic sounds are produced by expiration of air through tightly associated, but not vibrating chords (Fisher & Scharff, 2009). Mouse pups produce sounds as a reflex in response to altered arousal, e.g. when they are separated from the mother or their nest. The purpose of this behavior is to elicit retrieval by the parent, similar to a crying human baby. These isolation calls by themselves are sufficient to elicit parental retrieval behavior (Fischer & Hammerschmidt, 2011). Since these vocalizations are purely innate (Scharff & Petri, 2011), their suitability as a model for human speech is limited (Fischer & Hammerschmidt, 2011). In adulthood, males produce ultrasonic, multisyllabic courtship songs that are elicited by the presence of female mice or pheromones (Fisher & Scharff, 2009).

Several mouse models for FOXP2 have been used to investigate a potential function in the different kinds of vocalizations. Apart from knock-out mice, which completely lack one or both copies of the FOXP2 gene, also mutations resembling

the human cases were used. Groszer et al. (2008) used a mouse carrying the same mutation as the KE family (R552H) and observed a reduction in protein levels by 50%, mirroring the situation in the KE family. The authors observed that pups homozygous for the mutation were still able to produce audible calls, ultrasounds and clicks under high stress levels. The number of vocalizations was not different from wild type littermates, but more clicks and fewer ultrasounds (with lower sound pressure) were produced, although these might be secondary effects as a consequence of other problems (lung, developmental delay). These differences were not present in heterozygotes, the more appropriate comparison to the KE family, although different studies report that under less stressful conditions, these heterozygous mutant pups do not produce ultrasonic isolation calls (Shu et al., 2005; Fujita et al., 2008). In contrast, Gaub et al. (2010) report that both FOXP2 R552H and S321X (leading to the production of a truncated version of the protein) pups produce all sounds and show no significant differences to wild type that would exceed the normal variability. As mentioned above, these pup vocalizations are innate and for this and many other reasons not comparable to human speech. Potentially more informative is the investigation of an effect on adult courtship song, but this has not been carried out to date. In addition, clear evidence is missing if mouse song is learned in the same (imitiation based) way like human speech and birdsong and which brain regions are involved (Scharff & Petri, 2011).

In contrast to a relatively unaffected ability to produce vocalizations, Groszer et al. (2008) observed significant behavioral and physiological differences in FOXP2 mutant mice. They perform worse than their wild type littermates in motor tasks, consistent with impaired motor skill learning and affected frontostriatal and/or frontocerebellar circuitry and similar to the suggested motor function in humans.

Pup vocalizations were also investigated in a mouse carrying a humanized version of FOXP2 (Enard et al., 2009, see section 2.3.1). Although the authors observe slightly changed parameters in vocalizations, e.g. lower start, mean and maximal frequency, these were within the normal range of variation. In general, the

question remains, which aspect of sound production is actually affected (Fischer & Hammerschmidt, 2011).

In conclusion, no final assessment of a potential function of FOXP2 in controlling mouse vocalizations is possible. One main reason is that the data so far cannot be compared to human deficits, since it exclusively focuses on purely innate behavior, while speech involves voluntary control of learned vocalizations (Fisher & Scharff, 2009). Although mice carrying the KE mutation exhibit changes in neuronal plasticity in the striatum and – potentially associated with this – motor learning, less effects could be observed on the types of vocalizations investigated so far (Scharff & Petri, 2011). In general it can be concluded that "we should be wary of drawing simplistic correspondences between rodent pup vocalizations and human speech" (Fisher & Scharff, 2009, p. 172).

2.3.2.2 Songbirds

A more promising model system for human language – and here especially the component of vocal learning – is bird song. Both humans and songbirds interact vocally by selecting and arranging units ('syllables') into higher order structures ('sentences') in a rule-governed way (Fisher & Scharff, 2009). Apart from some important differences, there are a lot of similarities (cf. Fisher & Scharff, 2009, box 4), suggesting that insights into the neural basis and genetic requirements of bird song might be applicable to the human situation as well and therefore represent an experimental window into language competence. Only a few species are considered to have the ability for vocal learning (apart from humans these are mainly songbirds, bats, dolphins and elephants), which can be tested by depriving the animals of acoustic inputs during development and then monitoring the effects on the production of a "normal" and functional vocal output (White, 2010).

Birds learn their songs by imitating a tutor (Zeigler & Marler, 2008). They listen to the tutor's songs and their own vocal output and adapt the latter to fit the input (White, 2010). This process can be divided into distinct phases: In a "sensitive learning phase", young birds memorize the song of the tutor, without a lot of vocal output from the side of the learner. In the following "sensory-motor phase"

they try to imitate what they have heard and modify it using auditory feedback (Scharff & Haesler, 2005). Therefore, birdsong "has to be learned by integrating auditory input with vocal motor output through practice" (Scharff & Petri, 2011, p. 2133).

Certain areas in the brain of songbirds have been implicated in song recognition, production and learning, constituting the so called 'song system' (Fisher & Scharff, 2009). In particular, a specific nucleus in the basal ganglia, area X, is at the heart of this song system. Consistent with a potential function in the communication of birds, FOXP2 is expressed in cortical and thalamic regions implicated in birdsong and in the basal ganglia and in particular in area X (Schulz et al., 2010). In contrast, FOXP2 does not seem to be expressed in motor areas controlling the beak, tongue and oral cavity of birds (Haesler et al., 2004), suggesting that its function is not purely a direct control of movements of the speech organs, but rather in planning and orchestrating them.

FOXP2 expression in songbirds has been shown to reflect the pattern observed in humans (Teramitsu et al., 2004). Strikingly, FOXP2 expression in area X of young zebra finches is particularly high when they need to learn their song (Haesler et al., 2004). In contrast to zebra finches, who learn one song and keep singing the same song – with continuing quality control through undirected singing – for their whole life, canaries can remodel their song at the end of the breeding season in late summer and fall, which also implies plasticity in the underlying neural circuits (Scharff & Haesler, 2005) – potentially an evolutionary strategy for finding a more effective song for the following year. Haesler et al. (2004) showed that FOXP2 levels in area X specifically increase during this time of remodeling, suggesting a role for FOXP2 in the switch between phases of more and less plasticity in the song system (Fig. 2.18). This seasonal pattern of regulation of FOXP2 expression could be indirectly caused by changed environmental factors like daylight hours or seasonal behaviors (Scharff & Haesler, 2005). Acute changes in *FOXP2* mRNA levels in area X of zebra finches associated with singing have been observed by Teramitsu and White (2006). The authors show that this only happens in undirected singing, but not when the male sings to a female, ruling out that this is just an effect of the motor act. These results rather indicate an influence of the social context and

the purpose of the act, which in the case of undirected singing is rehearsal and adaptation of the song and thereby potentially linked to remodelling at the level of synaptic connections.

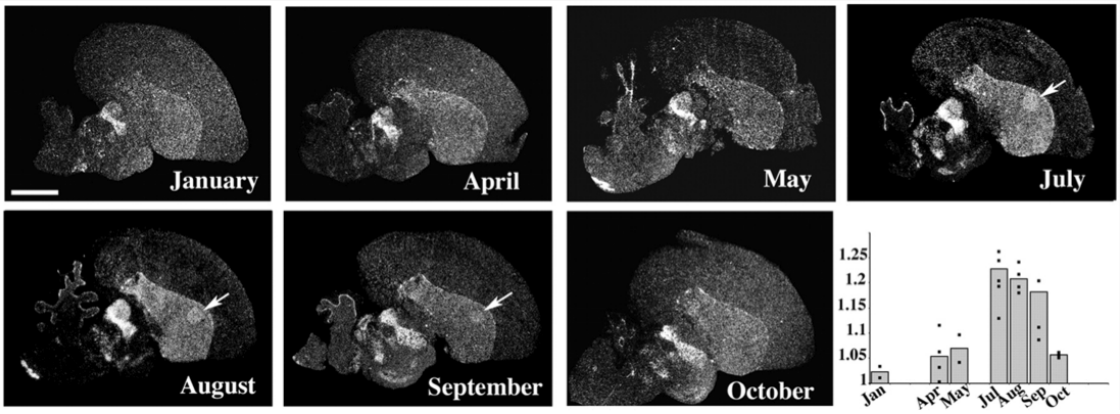

Figure 2.18: Seasonal variation of FOXP2 expression in area X of adult canaries. More FOXP2 is present between July and September, when song remodelling occurs (from Haesler et al., 2004, Fig. 5).

These studies investigated the presence of the RNA and correlated this with expression of the gene. The production of mRNA of a certain gene, however, is only the first step towards the final gene product and its function, so it still needed to be investigated, whether these claims also hold true for FOXP2 protein. Miller et al. (2008) generated a specific antibody for FOXP2 to reliably detect the protein in brain slices and brain extracts. The authors compared zebra finches that were distracted from singing for two hours to birds that showed a certain degree of directed or undirected singing and normalized the FOXP2 levels in extracts from area X to those in birds that were sacrificed immediately after lights-on and not monitored for 2 hours. Both directed and undirected singing led to a decrease in FOXP2 protein levels compared to non-singing birds, although it seems rather like an increase in FOXP2 protein (as seen in non singing birds compared to birds sacrificed immediately) was prevented by singing. In the case of undirected singing (associated with learning and auditory feedback), a weak correlation between the amount of singing and the downregulation of FOXP2 could be observed, but this

did not reach statistical significance. In light of the identification of FOXP2 target genes (although in mouse) that included genes involved in synaptic plasticity, a transient downregulation of their transcriptional repressor FOXP2 could allow for specific expression of genes involved in the formation of new synaptic connections or the tuning of existing ones and thereby formation of new memories or adaptation of existing knowledge on the cellular level, as would be required in the rehearsal process during song acquisition or maintenance. Fisher and Scharff (2009), however, raise concerns about the method used by Miller et al. (2008), stating that the amounts of FOXP2 protein were measured relative to a reference gene that is commonly used in this kind of studies, but for which it is not known if its expression might be affected by the absence or presence of singing and associated environmental conditions. In fact, Fisher and Scharff (2009) mention that in other brain areas, expression of this reference gene is in fact affected by singing, which would render the conclusions drawn by Miller et al. (2008) moot.

In any case, this correlation of FOXP2 expression with song learning and adaptation is strong evidence for a functional link between FOXP2 expression in area X and the bird's ability to imitate and diversify the tutor's song. To test this, Haesler et al. (2007) used an RNA interference based approach to downregulate FOXP2 levels specifically in area X of male zebra finches. This resulted in a reduction of FOXP2 by 50%, mirroring the situation in human patients suffering from heterozygous FOXP2 mutations (Fisher & Scharff, 2009). After downregulation of FOXP2 in area X, birds did not imitate their tutor's song completely and omitted several syllables from the input. Copying of the tutor's syllables was less accurate (Fig. 2.19), but with no common features being impaired and still being able to produce all of these features, but failing to imitate (Haesler et al., 2007), suggesting that there are no underlying articulatory difficulties that would prevent the birds from producing certain sounds (Fisher & Scharff, 2009). The song that was produced was more variable than in birds with normal FOXP2 levels in area X, which is also a characteristic feature of human patients suffering from FOXP2 mutations (Scharff & Petri, 2011; Watkins et al., 2002). This would suggest a role for FOXP2 in sensory-motor integration (Fisher and Scharff, 2009), but specific deactivation of FOXP2 during e.g. the sensitive learning phase and subsequent reactivation of

FOXP2 function would be needed to further dissect the role of FOXP2 in the different aspects of song learning, namely sensory, motor and sensorimotor integration (cf. Scharff & Petri, 2011).

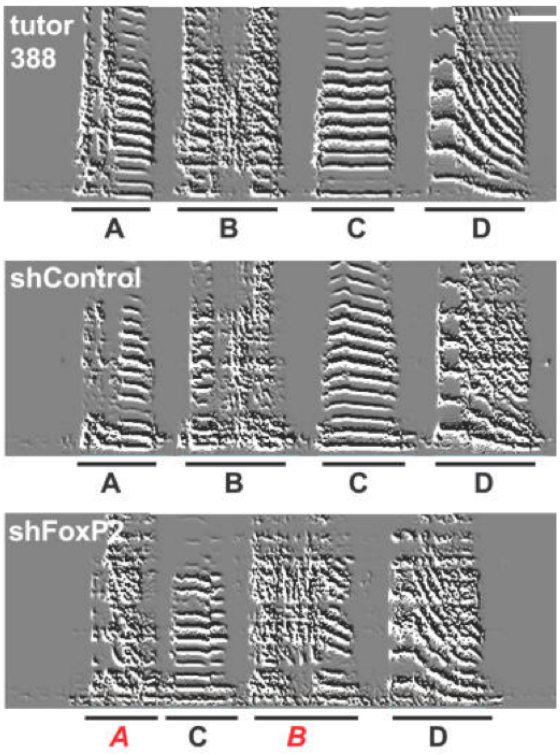

Figure 2.19: Representative sonograms from control and FOXP2 knock-down birds that had the same tutor. Both the order of individual elements and the imitation of the elements themselves (red italics) was affected (modified from Haesler et al., 2007, Fig. 3).

In trying to find the cellular correlate of this phenotype, Schulz et al. (2010) investigated area X on the cellular level. This brain region is largely composed of neurons with characteristics of mammalian medium spiny neurons, a cell type with an extensive dendritic tree accounting for approximately 90% of the neurons in the striatum. Area X spiny neurons are continuously renewed after birth, especially during the critical period of vocal learning, and express FOXP2. To determine whether FOXP2 is involved in the plasticity of spiny neurons, by regulating some steps of their continuous generation or by regulating their function, the authors

analyzed the effect of FOXP2 knock down on spiny neuron development and morphological plasticity.

Spiny neurons arise in the ventricular zone, where neuronal stem cells reside, and subsequently migrate to area X in the striatum. Downregulation of FOXP2 in neither the ventricular zone nor area X had a significant effect on the number of SNs or their recruitment and migration from the ventricular zone to area X (Schulz et al., 2010). Downregulation in both cases, the immature precursor in the ventricular zone and the mature spiny neuron in area X, however, led to reduced density of dendritic spines (Fig. 2.20), small structures on neuronal processes, where input from other cells is received and which are highly variable and are subject to modulation on the basis of neuronal activity. While the basic connectivity of brain regions, including area X, is completed at the time of the experiment, the effect of FOXP2 downregulation suggests that FOXP2 might be involved in the formation or maintenance of spines, which is in concordance with previous data on mice implicating FOXP2 in synaptic plasticity (Enard et al., 2009; Groszer et al., 2008). This hypothesis is also strengthened by the list of FOXP2 targets, and in particular the most prominent of those, CNTNAP2, which belongs to a family of proteins that localize to synapses and are involved in the formation and correct functioning of synapses (cf. Schulz et al., 2010).

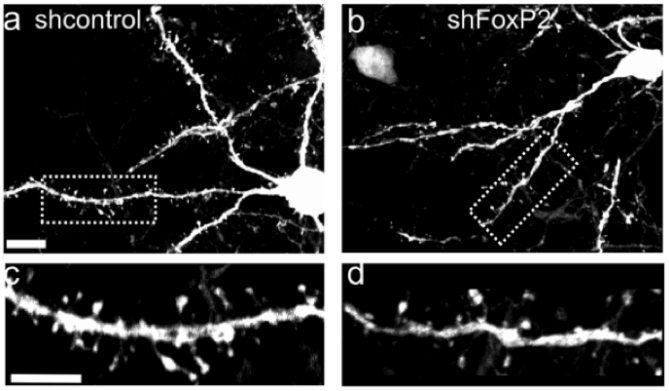

Figure 2.20: The density of dendritic spines (and thereby potentially also synaptic connections) in zebra finch area X spiny neurons is reduced upon knock-down of FOXP2 in (modified from Schulz et al., 2010, Fig. 5).

The evidence from song birds is an important indication that FOXP2 function is not only essential during development of language/song-related brain structures, but also has an effect in the functioning and modulation of these circuits in the adult bird. It was suggested that this gene serves as a "plasticity gate" in relevant brain areas, where high levels correlate with song stability and low levels with plasticity and variability (Graham & Fisher, 2013; Teramitsu et al., 2010).

2.4 FOXP2 – a language gene?

The discovery of a family showing simple Mendelian inheritance of a specific language deficit raised hopes that this would be an entry-point to the discovery of the genetic basis of human language competence. The fact that the pattern of inheritance indicated a single affected genetic locus suggested that it might be possible to narrow down this basis to a single gene. Such a functional relation of a single gene with a cognitive trait of immense complexity would be very exceptional, as it is becoming more and more clear that even the – compared to language competence as a whole – simplest biological process usually involves a plethora of genes and biochemical pathways. Following the discovery of the forkhead box transcription factor FOXP2 as the gene responsible for the language deficits in the KE family (Lai et al., 2001) and similar cases, many research groups tried to answer the question, what molecular mechanisms were influenced by FOXP2 and how these functions could relate to the language impairment. These studies revealed an involvement of FOXP2 in the development and patterning of certain parts of the central nervous system, which seems to be highly conserved throughout evolution. In addition, also regulated alterations in synaptic connections in the adult brain seem to be potentially under the influence of FOXP2, providing a link between this gene and learning-based plasticity of the brain, which is a cellular basis for language acquisition and use. Despite all this encouraging findings, the basic question remains: Is FOXP2 really a key player in the biological basis of human language competence? Is it a – or even the – language gene?

2.4.1 Requirements for a language gene

To answer this, it is necessary to define what the requirements for the status as a "language gene" are. Strategies to find a language gene have already been discussed in chapter 1. In this section, I would like to point out what can be expected from a "language gene" and which concepts are rather unrealistic in the light of the knowledge about the biological basis.

Functional specificity Biological processes – and language competence ultimately has to be seen as such – do not necessarily follow scientific classifications. The human body functions as a whole, and biochemical pathways are highly interconnected and usually serve multiple functions at the level of observation. One obvious example is the supply of a cell with energy to exert its function, which follows the same principles for a muscle cell, a hepatocyte and a neuron, but the consequences of malfunctioning will result in very different symptoms. Although the sustained energy supply of a cell is a prerequisite for its function and its absence might in the case of the brain surface first as a deficit in higher order brain functions – which notoriously are prone to be affected first as a consequence of their sensitivity and the fact that they rely on functioning of many brain regions at high level. These deficits, however, would not fulfill the criterion of functional specificity and a gene that exerts the same function in every tissue can therefore not be considered a "language gene".

Necessity The most obvious requirement for a language gene is its importance for language function. Perturbations or loss of a language gene should have severe consequences for language production and perception. In this case, a (specific) effect on all aspects of language competence is highly unlikely. There will rather be subsystems, that are more – or exclusively – affected, indicating that this gene might be necessary for a particular aspect of language competence – the only scenario that is possible to envision keeping the basic principles of the functioning of biological systems in mind.

Relevance The fact that a gene has a function in a given neuronal circuit does not imply that it is also necessary for a particular task of this group of cells. In the case of language, even a specific and necessary function in a language-related brain region does not have to be functionally linked to the role of this area in language processing. A specific impairment of these cells in language-related processes (ideally with otherwise largely intact morphology and functionality) would be a good indication for the functional relevance of this alteration.

Sufficiency The criterion that is most difficult to fulfil is the requirement for this gene to be – to some extent – able to trigger specific changes or induce relevant transformations. This criterion will usually be of course only partly met, since if it were 100% sufficient to add a certain function to the system, this would imply that it is indeed the only factor necessary for a certain function, which – as mentioned above – in the case of a complex trait such as language is highly unlikely. On the other hand, exclusively negative evidence for the involvement of a gene (i.e. only proving that it is necessary) could raise doubts about the relevance and functional specificity for the process under investigation. Evidence for morphological and functional changes induced by exchanging mouse FOXP2 with a humanized version (Enard et al., 2009) thus strengthens the role of FOXP2 in language relevant brain areas and presents it not just as a requirement, but also as a potential inducing factor for changes that could be relevant for language processing in the human brain.

2.4.2 What is the function of FOXP2?

In the following, the putative functions of FOXP2 will be summarized based on the presented literature. The basic explanation of FOXP2 function has to start at the molecular level, which underlies all the other roles it plays in the functioning of the organism. The next level of analysis has to be the tissue the gene is active in and its role in this context. Ultimately, the functions on the cellular and tissue level have to be linked to the effect that malfunctioning of this gene has on the performance level. All three levels together potentially provide a link from the molecular function

of a single protein (and in the case of the KE family, the importance of a single building block of this protein) to its role in social interaction and higher cognitive functions.

2.4.2.1 On the cellular level

As described above, FOXP2 belongs to a group of proteins that – by binding to a specific DNA sequence – can regulate the expression of target genes adjacent to this binding site. Recruitment of FOXP2 to a given target gene thereby functions as a molecular switch to turn this gene on or off. Transcription factors are highly regulated during the development of an organism, and subsequent and/or combinatorial activation of different transcription factors can guide the differentiation of a stem cell via intermediate stages to one of several possible routes of differentiation, i.e. to adopting one or the other cell fate (e.g. cf. Knoblich, 1997; Busslinger, 2004). Therefore, the molecular function of FOXP2 as a regulator of expression of a potentially wide variety of target genes could very well be involved in regulating the development of very specific networks in the brain. In this context, especially the identification of FOXP2 target genes has been of great importance and future research further validating these targets can be expected to give exciting new insights into the regulation of development of language-relevant brain areas. Among these targets, CNTNAP2 has up to now attracted most attention, since it had already before been implicated in disorders also affecting language competence. In addition to this obvious candidate, genome-wide studies discovered several genes regulating axon outgrowth and pathfinding among the targets of FOXP2. Given that information storage and processing in the brain (and integration of several inputs in general) relies on precise connections between neurons in distant brain regions, precise regulation of this connectivity is of course of utmost importance for the correct functioning of the brain. Other potential FOXP2 targets argue for a function in activity-based modifications of neuronal connections, in line with data from songbirds showing FOXP2 expression depending on the requirement to learn new songs (White, 2010). These findings also emphasize that FOXP2 not only has a role in the formation of the nervous system, but also in the subsequent maintenance and fine tuning of synaptic connections, as would be expected for a "language

gene". To what extent the proposed model for FOXP2's function in songbirds also holds true in humans and if FOXP2 is differentially regulated in the learning and rehearsal of oromotor sequences still has to be investigated. In general, it remains to be elucidated, how specific the effects of over- or underactivation of some of these genes could be to language, but they constitute promising candidates for a molecular prerequisite for higher order brain functions. Fisher and Scharff (2009), for example, put forward one hypothesis, in which FOXP2 "normally acts to modulate neural plasticity in relevant circuits by repressing genes that are typically induced by neuronal activity" (p. 176).

Concerning the criteria for a language gene presented above, the functional specificity of the transcription factor FOXP2 for language crucially depends on the target genes and the cellular context where this regulation happens. The data so far would indicate that the target genes are potentially specific enough to explain a given deficit without a global effect on the organism. On the other hand, the FOXP2 target genes will most likely not exclusively be involved in forming the cellular basis of language in the brain, so that the specificity in this respect might come more from the degree and timing of regulation (i.e. in what way the levels of these target genes in the cell are affected by FOXP2 and if this has to happen at a certain developmental stage) than solely from the identity of the genes. The criteria of necessity, relevance and sufficiency can only be fully evaluated once the contributing downstream components are known, but already the data available to date indicate, that the presence of functional FOXP2 is necessary for the regulation of its target genes, as many of these showed altered expression levels upon loss of FOXP2 (Spiteri et al., 2007; Vernes et al., 2007). In addition, the introduction of humanized FOXP2 into mice and subsequent changes in the expression of certain genes (Enard et al., 2009) indicate that FOXP2 (and even more precisely the human version) might be indeed sufficient to induce specific changes in gene expression. Whether these particular changes are relevant for language competence is at this point only subject to speculation.

2.4.2.2 On the tissue level

The most informative level of description of FOXP2 function might be the tissue level, as this constitutes the link between the cellular function of this gene and the deficits at the surface. On the one hand, information on where FOXP2 is expressed, i.e. where it could have a potential function, is the starting point for describing FOXP2's role at the tissue level. Several papers showed (Ferland et al., 2003; Lai et al., 2003; Takahashi et al., 2003; Teramitsu et al., 2004; Takahashi et al., 2008) that its expression seems to be highly conserved, arguing for an important – although not necessarily identical – function across species. The hotspots of FOXP2 expression in the brain are the inferior frontal cortex, including Broca's area in humans, parts of the precentral gyrus (especially the ones responsible for orofacial muscle control), parts of the thalamus, the cerebellum and the striatum, in particular the caudate nucleus. This correlates to a large extent with regions of changed microarchitecture and areas where functional imaging revealed differences in activation patterns between individuals with wild type or mutant FOXP2. In addition to changes in the regulation of transcriptional targets, the humanized version of FOXP2 in mice also leads to subtle anatomical changes and differences in synaptic plasticity. Both the loss-of-function (mutant) and the gain-of-function (humanized FOXP2 in mice) condition would indicate that FOXP2 has a necessary role in the development of these brain areas (also other FOX family members are known to be involved in the structural formation of anatomical regions (Carlsson & Mahlapuu, 2002)) and also has the potential of influencing this development and the plasticity and functioning of the final state, with all other factors involved being unchanged. This is a remarkable finding and despite a lack of more precise knowledge about the contributions of the individual brain regions can be expected to have a functional relevance for the observed phenotype, but also here a one-to-one matching with the deficits at the performance level is missing.

What hypotheses can be built from the expression pattern and the regions with (functional) anatomical differences? As one of the classical "language areas" in the brain, Broca's area is the most obvious candidate for a role of FOXP2 dependent brain structures in language processing. In line with this model, functional imaging

studies showed a lack of activation in Broca's area in the left hemisphere in a verb generation task (Liegeois et al., 2003). Brain imaging revealed also a reduction in grey matter in Broca's area and parts of the premotor cortex, which was in contrast to an increase in Wernicke's area (Belton et al., 2003). This could indicate that, while auditory information can be transduced normally to Broca's area, there is a reduction in information flow from Broca's area to the motor cortex, in line with the impaired fluency and fine motor movements of speech organs in affected members of the KE family (Cooper, 2006).

The cortex is organized in different cell layers. The lower layers which have formed first during brain development express FOXP2 and are the ones that also form connections to subcortical structures. Therefore, a reduction of FOXP2 could in this context lead to the observable reduction in grey matter and presumably a loss of connectivity with subcortical structures (Cooper, 2006). Established subcortical "targets" of these projections are the basal ganglia, especially the striatum consisting of the caudate nucleus and the putamen. These are regions located deep within the brain, whose functions were first elucidated by surgical interventions in Parkinsons disease patients (Marsden & Obeso, 1994). Their main function supposedly is to support the execution of cortically initiated movements and to suppress unwanted muscle activity (Lieberman, 2006). Basal ganglia are also referred to as the sequencing engine of the brain and as the basis for reiteration allowing humans to produce a potentially infinite number of sentences from a finite set of words and syntactic rules.

Given the fact that the basal ganglia circuitry regulating motor control does not radically differ from that implicated in cognition, Marsden and Obbeso (1994) conclude that

"the role of the basal ganglia in controlling movement must give insight into their other functions, particularly if thought is mental movement without motion. Perhaps the basal ganglia are an elaborate machine, within the overall frontal lobe distributed system, that allow routine thought and action, but which responds to new circumstances to allow a change in direction of ideas and movement" (p. 893).

According to Lieberman (2009) human FOXP2 could therefore function to "enhance the efficiency of neural cortico-basal ganglia circuits, the brain mechanisms that in humans are known to regulate motor control including speech, word recognition, sentence comprehension, recognition of visual forms, mental arithmetic, and other aspects of cognition" (p. 800). FOXP2 anomalies may then disrupt or negatively influence the development of basal ganglia and in particular cortico-basal ganglia circuits and thus cause deficits in speech production and cognitive flexibility.

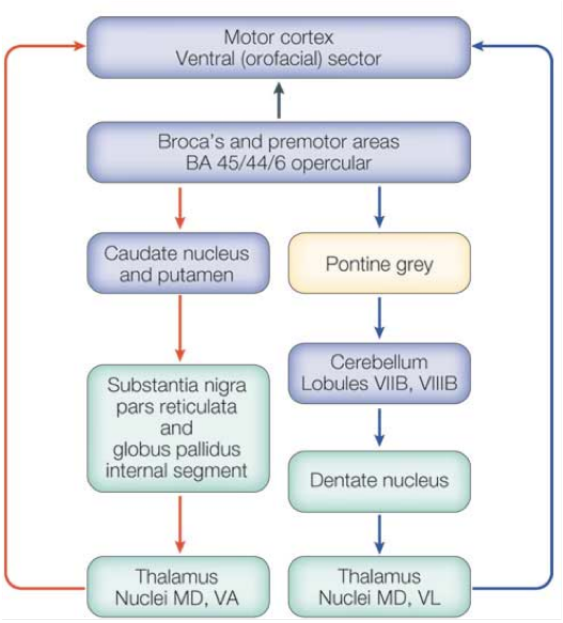

Figure 2.21: FOXP2 dependent speech and language circuit. Blue: structurally and/or functionally affected in KE family members carrying a mutated FOXP2 gene; blue and green: FOXP2 expressing; BA = Brodmann area, MD = medial dorsal, VL = ventral lateral, VA = ventral anterior (from Vargha-Khadem et al., 2005, Fig. 4).

Based on the evidence from different studies, Vargha-Khadem et al. (2005) propose a model for a FOXP2 dependent circuitry in the brain that is the basis – or at least a basic requirement – for language competence (Fig. 2.21). It is based on the similarity to the regulation of other motor functions and the neural expression

pattern of FOXP2 and postulates three pathways, how the activity of the orofacial portion of the motor cortex can be modulated by Broca's area, both directly and via subcortical structures. Almost every component of these pathways expresses FOXP2, providing an explanation for the verbal dyspraxia of KE family members, but also for the functional contribution of FOXP2 to the emergence of language abilities.

Vargha-Khadem's model is focused on the motor function and the orofacial deficits. Bearing in mind the other functions of the basal ganglia and Broca's area and also the impossibility to clearly separate motor from cognitive circuits, however, this could very well also hold true for a function of FOXP2 on a more conceptual level of language production. This hypothesis is in line with the assumption that there are both cognitive and motor pathways connecting the human cortex with the basal ganglia and the cerebellum (Middleton & Strick, 2000). In the case of the cerebellum, data from fMRI studies suggested that apart from its function in sequencing of syllables during overt language production, it is also involved in internal speech with potential roles in memory and thought processes (Ackermann, 2008). In this context, the human specific alterations in FOXP2 might have been a critical component in the development of a sequencing engine for linguistic units in the brain.

Campbell et al. (2009) build on these models and propose three major pathways that are all dependent on processing in the thalamus, the major relay station in the brain, and involve both cortical and subcortical inputs:

- Modulation of fine motor actions by the striatum
- Modulation of the timing of motor actions by the cerebellum and the olivary nuclei
- Integration of auditory and visual input by the thalamus

Although these pathways are not specific to vocal communication, they will have a strong influence on it, and given the role FOXP2 is playing in the development and functioning of these structures, "we may gain a more complete appreciation of the nature and specificity of its contributions to adult behaviors. Such work would

deepen our understanding of vertebrate vocal communication and its relationship to human language" (Campbell et al., 2009, p. 97).

Enard (2011) suggests that these pathways are not generally necessary for language production, but more specifically "for inferring statistical regularities when parsing speech, learning motor sequences, learning artificial grammars or learning categories" (p. 420), which would be consistent with the rather specific impairments of patients with reduced functional FOXP2.

Similar cortico-basal ganglia pathways are of course present in many other species. Interestingly, songbirds have developed a specialized cortico-striatal circuit that is very similar to the mammalian one. This so called anterior forebrain pathway is necessary for song learning, where vocal motor patterns leading to an output that is most similar to the template song are reinforced by this pathway – analogous to the role of mammalian cortico-basal ganglia circuits in reinforcement of learning by imitation (cf. Enard, 2011) – and expression of FOXP2, especially in the striatal component of this pathway, seems to be essential for this (Haesler et al., 2007). Reimers-Kipping et al. (2011) speculate that during the evolvement of vocal learning, adaptations in cortico-striatal circuits need to occur and this happened in humans and in songbirds (and possibly other species) independently. The fact that FOXP2 has been implicated in both cases further underlines its importance for the adaptation of these pathways for more sophisticated functions, exceeding the mere control of motor output.

Based on the models for FOXP2 dependent circuitry (Vargha-Khadem et al., 2005; Campbell et al., 2009; Reimers-Kipping et al., 2011) conclude that the central deficit in FOXP2-related speech and language disorders in humans would lie in a malfunctioning of cortico-basal ganglia and cerebellar circuits, which are both crucially involved in the sequencing and fine-tuning of movements (Middleton & Strick, 2000). Although the same circuits are present in other species and can also be found in patients with only one functional copy of the FOXP2 gene, normal levels of human-specific FOXP2 might be necessary to bring the cortico-basal ganglia circuits to a "state of higher efficiency" in humans, possibly allowing for the evolution of human specific language abilities (Lieberman, 2009).

FOXP2 has been shown to be necessary for normal development and functioning of these cortico-subcortical pathways, and the human version of FOXP2 can affect the connectivity and plasticity of this circuitry, but whether this function is sufficient to explain the human-specific level of language competence is still unclear. As long as the neural mechanisms underlying speech and language are not fully understood, it cannot be evaluated to what extent a potential "language gene" is necessary (or sufficient) for their development and functioning. In reverse, the identification of relevant brain structures (especially on the level of neuronal microarchitecture and wiring) is to a large extent dependent on the discovery of genes necessary for the correct functioning of these areas, which bears the danger of using circular arguments when making strong claims about a potential language gene.

2.4.2.3 On the performance level

In evaluating the function of FOXP2 on the performance level (in most cases using evidence from reduced FOXP2 functionality), two contrasting positions can be observed. On the one hand, deficits following FOXP2 mutations have been characterized as specific to language, or even a subsystem or a particular process of language competence or grammar, e.g. Gopnik's (1990) postulation of feature blindness as the underlying deficit in members of the KE family. Other researchers, e.g. Vargha-Khadem, however, argued that also other areas of grammar were affected, and that the linguistic deficits were just a consequence of problems with articulation and an orofacial dyspraxia. Dominguez and Rakic (2009) remark that "the most obvious consequence of loss of function of FOXP2 in humans and rodents is impairment of motor skills and coordination. Problems in motor sequencing actions or procedural learning (the acquisition of fine motor skills) including those related to the mouth and face, thus can manifest as disorders of speech and language" (p. 169). In contrast to this, other orofacial motor functions that also involve the concerted action of many muscles, like swallowing, appeared to be unaffected, leading Lai et al. (2001) to state that nonverbal deficits cannot be considered characteristic of this disorder. Also Scharff and Haesler (2005) conclude from the biological data generated following the discovery of the FOXP2 gene, that these do not support "the

original suspicion that FOXP2 would be primarily involved with control of orofacial muscles" (p. 699). Instead, the nature of the affected circuits in humans and the analogy to songbirds would suggest a function in "sensory-motor integration important for sequenced behaviors and procedural learning" (Scharff & Haesler, 2005, p. 200). The latter is thought to underlie the rule-governed processes that assemble linguistic units into words, phrases and sentences by a "basal ganglia-dependent procedural memory system" (Scharff & Haesler, 2005, p. 200).

In a complex trait such as language, evaluating the contribution of single components becomes almost impossible. The consequences of a reduction or loss of FOXP2 in humans and other species suggest that it is a prerequisite for the correct functioning of some aspects of a vocal communication system. This role seems to be relatively specific to language, as most researchers state that language impairments are the leading and most characteristic symptom of FOXP2 associated disorders. Given that these symptoms are strikingly similar across patients and etiological mutations, it seems valid to assume that there is a specific contribution of FOXP2 to these symptoms. On the other hand, the majority of the cases of language impairment are not associated with FOXP2 mutations, indicating that even if a FOXP2 mutation can cause the observed deficits, mutations in other genes can have the same effect.

2.4.3 Conclusion

Despite a lot of research on FOXP2 that has been carried out over the last decade the question if it is a "language gene" is still unresolved and dependent on the definition of the term. It can certainly be seen as a gene necessary for the correct functioning of language processing in the brain and in this respect it can constitute a valuable entry point into studying language at the molecular level. FOXP2's function as a transcription factor suggests that there are potentially more specific target genes that could be mutated themselves or whose expression might be altered (in a FOXP2 dependent way) by changes in their regulatory sequence, opening new perspectives and strategies for the discovery of genes underlying language competence. It is, however, likely that there will not be one target of FOXP2 that is

alone responsible for the language specific functions, but rather a network of target genes. Evidence of modulated FOXP2 activity in song birds corresponding to the need for learning new songs or maintaining already acquired ones (Miller et al., 2008) suggests that a similar modulation could happen in humans and for example affect specific cellular functions via changes in the expression of certain target genes.

FOXP2 could also provide insight into the evolution of human language competence, in regard to both the genetic and neural basis of what makes us human (Lieberman, 2006). While other regulatory genes undoubtedly are involved in the evolution of human language and cognition, research on FOXP2 can advance our understanding of the nature of the neural basis and the time course of the evolution of these human qualities (Enard, 2011). Scharff and Petri (2012), however, warn that despite all the promising evidence from different model systems the question "whether FOXP2 played a role in bringing about circuit changes that facilitated the emergence of human language" (p. 2134) is still far from resolved. A complex trait like language necessarily has to be polygenic, and other important factors might not be present or active in the same way in other systems.

In the human lineage, two specific amino acid substitutions have been reported and these changes have been proposed to have functional implications (Enard et al., 2009). Enard (2011) speculates about possible effects on cortico-basal ganglia circuits and proposes a change in the function of these pathways in reinforcement during learning, in concordance with the fact that these structures do not seem to be absolutely indispensable for adult language processing, but for language acquisition, where "they are important for inferring statistical regularities when parsing speech, learning motor sequences, learning artificial grammars or learning categories" (Enard, 2011, p. 420). A change in FOXP2 activity, comparable to the seasonal changes in song birds or alternatively by different target specificities on the DNA level, could modulate these structures in a way, that they become more adapted to acquiring a complex vocal communication system, with effects on both the cognitive level and the actual execution of fine motor programs. These changes would therefore enhance language-specific learning mechanisms in the course of

evolution, a view that also Reimers-Kipping et al. (2011) see as a plausible scenario.

In a general assessment of the data available at this point, the caveat raised by Marcus and Fisher (2003) that *FOXP2* cannot be called 'the gene for speech' or 'the gene for language', seems to be justified. It is just one element of a complex pathway involving multiple genes and neither FOXP2 mutations per se nor the oromotor deficits observed in the KE family and other patients are common in developmental language disorders. Instead of speaking of FOXP2 as "the language gene", a more adequate assessment of its function in different species and its significance for research on the biological basis of language might be, following Scharff and Haesler (2005), that "the accumulated knowledge encourages cautious optimism that studying FOXP2 function will help us to understand the neural mechanisms of learned vocal communication" (p. 700).

3

Language genes and the innateness debate

3.1 Introduction

Throughout history language has been employed as a defining characteristic of the human race and has been seen as a distinguishing feature between man and „beast“. It is often considered a unique cognitive faculty that „most clearly sets our own species apart from the rest of animals“ (Nadal et al., 2006, p. 187). But what enables us to use a communication system, whose complexity by far excedes any other form of communication found in the animal kingdom?

It is and always was tempting to speculate about the nature of biological predisposition of humans to develop this kind of cognitive abilities. Although there

has been a long-standing philosophical debate over innateness of ideas and knowledge (cf. Samet, 2008), in the context of language this only started in fairly recent times around 1900, when researchers realized that language was not only connecting a word with a concept, but constituted a complex system of how to put words together (Cowie, 2010). This question was not only a philosophical one, but also entered the fields of natural sciences, giving rise to a new discipline that from the 1970s on started to be called „Biolinguistics“. Modern biolinguistics began as a collaboration between biologists and linguists and tried to connect linguistic concepts with a biological basis (Di Sciullo et al., 2010). This includes very general questions about the neural mechanisms supporting language use and their genetic correlate and the specificity of these in the context of cognition and evolution (Nadal et al., 2006), but also extends to very specific problems. One example, cited by Di Sciullo et al. (2010), concerns Chomsky's theory of generative grammar. In the paradigm of the minimalist program (Chomsky, 1995), the operation Merge „glues“ two individual units (e.g. words) together to form a more complex structure (e.g. a phrase). It thereby takes two components from the same hierarchical level and selects one of them to be the dominant one, so that the resulting complex inherits some properties of this dominant daughter, the so called head, and enables the formation of structural differentiations. According to Di Sciullo et al. (2010), „a central goal of biolinguistics is to characterize the biological properties of this recursive operator, beginning with its abstract properties, ultimately arriving at its concrete biological instantiation“ (p. 4). Several parallels to biology can be found here, like the recursive nature of this operation and the inherent asymmetry of this operation that can be seen as resembling cellular asymmetries in developing organisms

This analogy to biology, however, can merely be a metaphor or a way of describing the concept of asymmetry, but will not have any explanatory power, as the (genetic) factors guiding asymmetry in cells will not be the same that underlie the property of selecting one of two grammatical units as the head. Nevertheless, it exemplifies the ultimate goal of biolinguistics: To treat linguistic operations the same way as biological processes, since both occur in the same organism and are – at some level of observation – predetermined by the genetic program of this organism.

Along the same lines, Cullicover and Jackendoff (2005) stress that if grammar "is innate, it must be coded genetically, just like any specialized cognitive capacity in any animal, such as bat sonar" (p. 13).

Before trying to address very specific problems like the biological instantiation of a grammatical operation, however, more general questions have to be answered (as formulated by Pinker and Jackendoff (2005, p. 202)):

- "Which aspects of the faculty are learned from environmental input and which aspects arise from the innate design of the brain (including the ability to learn the learned parts)",
- "what parts are specific to language and which belong to more general abilities",
- "which aspects are uniquely human and which are shared with other groups of animals"?

As a first step, however, it needs to be laid out how the concept of innateness is understood in various contexts and disciplines.

3.2 Defining innateness

In following the innateness debate, it soon becomes clear that not all concepts of innateness are the same, but that this expression is used in a variety of ways (for meanings in behavioral science cf. Bateson, 1991). Following a common view in biology, "characteristic C is innate in some organisms if the genes in that organism program the developmental process to produce C" (Godfrey-Smith, 2007, p. 63). The characteristics that are the object of research in genetics and to which this statement usually applies are basic biological building blocks and not at the level of cognitive traits, and therefore, "the 'programmed for' traits [are] too low-level to be of interest to nativists" (Godfrey-Smith, 2007, p. 66).

In general, one main difference between the various definitions of innateness is whether a trait is innate at the level of genetic predispositions, i.e. if the starting

point of the implementation of this trait is already genetically encoded and non-variable, or if the same end state is reached under diverse environmental conditions, i.e. there is variability in the system, but backup or adaptation systems ensure that the end result will be the same.

In one extreme view following Konrad Lorenz' presentation of instincts as the innate traits par excellence, a trait cannot be seen as innate, if it needs any contribution from the environment for its normal development (cf. Tucic, 2002). Innate, genetic traits would therefore need to be "ontogenetically fixed", i.e. all the necessary information is found in the genotype. In the context of differences between individuals this view would entail that for an innate trait "phenotypic differences [...] in a given population can be explained by genetic differences" (Tucic, 2002, p. 99).

Closer to the first view, Godfrey-Smith (2007) states that "[t]he innate traits of an organism are the ones that are coded for, represented, informationally specified, or programmed for, by the organism's genetic endowment. The characteristics that are not coded for (etc.) are not innate, but acquired" (p. 56). While here the genetic predisposition is emphasized, Samuels (2004) follows a teleological view and defines „a cognitive mechanism, representation, bias, or connection to be innate to the extent that it emerges at some point in the course of normal development but is not a product of learning" (p. 58). He remarks that being innate is about robustly getting to an end-state, not about the way one comes to acquire something. Following this definition, something could well be both innate and learned (if both are involved in robustly getting to an end state). According to Stich (1975), something is innate when it appears in the normal course of development, i.e. it is part of the normal phenotype of this organism. Along similar lines, Ariew (1996; 1999) sees innateness as developmental canalization, a term coined by C. H. Waddington (1942), which implies an "insensitivity to environmental circumstances" (Godfrey-Smith, 2007, p.5). In this view, „a trait of an organism (with a given genotype G) is innate to the extent that it is environmentally canalized in organisms with G; and the trait is highly canalized to the extent that its development is insensitive to the range of environmental conditions under which it emerges" (Samuels, 2009, p. 333). Samuels (2009) points out that this definition depends on what is taken as

relevant environmental variability, and the definition of nativism therefore becomes a methodological problem.

Innate traits are often located at the basis of psychological theories (Cowie, 1999; Samuels, 2002) functioning as "psychological primitives", which are building blocks of psychological theories, but which themselves cannot be explained by psychology.

In contrast to a widespread opinion, innate traits are not the ones that are present at birth, which is neither necessary (innate characteristics can be acquired late in development) nor sufficient (learning before birth exists) for innateness (Samuels, 2009).

Sometimes the concept of innateness is invoked to limit the explanatory range a theory has to cover. Griffiths (2002) defines innate as "something that can be taken as given with respect to the set of causal factors currently under investigation" (p. 73). In the case of language the causal factors considered are psychological ones, and the actual factors involved could be biological. According to Samuels (2009) this usage of innateness also constitutes a way to avoid the need for detailed explanations, which also makes it susceptible to criticism.

Griffiths (2002) himself is especially sceptical about the "vernacular concept of innateness" that to him is an "expression of folk essentialism", a "pre-scientific thought" about the characteristic manifestations of "human nature", which – although "inconsistent with the Darwinian view of species", is a "widespread cognitive trait" (p. 73). Given the inherent vagueness of the term "innateness", he argues to disregard it in scientific writing and substitute it with different expressions that refer to the special kind of innateness – be it the genetic predisposition or just the fact that something is found in every individual (universality).

Wimsatt (1986; 1999) sees innate traits at the basis of many features of an organism, which makes these traits essential for normal development. Even complex cognitive traits are sometimes defined as solely being the products of internal, genetic causes, although this might not reflect the real situation and the widely accepted view is that cognitive traits can be a mix of internal and environmental factors (Samuels, 2002). Any radical view of innateness based on ontogenetic

fixation can also be refuted by research in genetics showing that most of the development of an organism is – at some level – guided by the interaction of genes and environment (Tucic, 2002).

Godfrey-Smith (2007) summarizes the options for the use of the term innateness in this scientific context:

- Innateness in the same sense as used in biology (including the concept of canalization (Waddington, 1942; Ariew, 1996))
- Cluster concept or family resemblance (Mameli & Bateson, 1996; Cowie, 2009)
- Innateness as a disciplinary marker: Samuels (2002) states that to be innate is characterized by the fact that its development cannot be described in psychological terms. According to Cowie (1999) being categorized as innate often indicates "metatheoretic pessimism", i.e. it is seen as impossible to find a naturalistic explanation for a trait.
- Proponents of a view termed ElimiNativism (coined by Cowie (2009)) argue to disregard this concept altogether in the scientific debate. Griffiths (2002) is equally critical of the concept of innateness. This standpoint constitutes, according to Godrey-Smith (2007), the most hostile treatment of innateness and ascribes it to a "folk biological mode of thinking".

Even researchers that make use of the concept of innateness remark that it is a confusing notion, since it conflates different ideas (e.g. Bates, 1994; Griffiths, 1997; Bates et al., 1998; Griffiths, 2002). In the following, the diverse approaches to innateness and its role in an explanation of human language competence will be discussed.

3.3 Different approaches to innateness

In trying to find a comprehensive account for human cognitive abilities, there are different paradigms researchers and philosophers subscribed to. In general, there

are two positions, which have been associated with different terms: focusing on innate, genetically determined properties („nature“, nativism, biological determinism (Tucic, 2002)) or emphasizing the role of the environment and personal experiences („nurture“, empiricism, behaviorism, social constructivism (Tucic, 2002)). These two frameworks are not necessarily mutually exclusive, and there are many shades of gray that specify positions in between strong nativism and empiricism, where biological and environmental factors are both thought to contribute to the outcome, an approach known as interactionism (Tucic, 2002). Within the interactionist framework, it is possible to distinguish two classes: simple interactions (black and white makes grey) and emergentism, implying that something completely new and unpredictable forms (Bates et al., 1998). While according to Bates and colleagues some emergentist standpoints have not been too convincing, recent neurobiological insights into the extraordinary plasticity of the brain strengthen the point of emergentism.

When language came into the focus of attention of scientists and philosophers, the everlasting debate on what can be attributed to nature and what to nurture or, in other words, what is innate and what is acquired, has been applied to the study of language.

In the first half of the 20thcentury the biological foundation of language was not a popular subject for research because learning and conditioning were seen as more important in this respect than genetic factors (Ganger & Stromswold, 1998). Skinner (1957) was one of the first to propose an elaborate theory of language acquisition. In Skinner's framework, knowing a language meant having a defined set of „behavioral dispositions“ that would, for example, in response to feeling cold as a result of an open door lead the individual to utter: please close the door! (cf. Cowie, 2010). Learning a language thus merely consists of „acquiring that set of dispositions“ through interaction with the environment: „A child acquires verbal behavior when relatively unpatterned vocalizations, selectively reinforced, gradually assume forms which produce appropriate consequences in a given verbal community“ (Skinner, 1957, p. 31). The child therefore is the passive subject of “operant conditioning” and language is acquired by reinforcement of randomly

occurring behaviors (Skinner, 1957), excluding any innate knowledge apart from general learning mechanisms.

In a reply to this theory, Noam Chomsky (1959) criticized Skinners arguments and stated that language is not just a set of verbal behaviors, as it is stimulus independent (any words can be used in reponse to a stimulus) and historically unbound (not determined by a history of reinforcement). In addition, Chomsky refutes that language acquisition would be conditioned at all (Chomsky, 1959; Cowie, 2010). The new aspects of this view were that (conscious) knowledge was attributed to the speakers and that children learn language on their own, challenging the prevailing idea that all learning involves reinforcement (Cowie, 2010).

To explain what it is that enables humans to speak, Noam Chomsky and others (Chomsky, 1965; Pinker, 1994; Anderson & Lightfoot, 2002) postulated a language organ (also referred to as module or faculty) in the brain. This contains „innate knowledge of linguistic rules, constraints and principles; this innate knowledge constitutes the 'initial state' of the language faculty“ (Cowie, 2010). During the phase of language acquisition the child is exposed to linguistic input, so called primary linguistic data (pld) that helps the child to modify this initial state in a way characteristic of a given language, leading – by the end of this process – to the final state of the language faculty: a fully developed language competence.

One characteristic feature of the language faculty is that it is not merely a storage space for corpora of words and phrases, but that it can actively produce novel items that have not been part of the input the individual received, thereby enabling us to produce an infinite set of utterances, which was not possible with the assumption of a necessarily finite corpus as postulated by behaviorists and structuralists (Cowie, 2010).

Two views of language learning can be observed within the Chomsky paradigm over the years: first (e.g. Chomsky, 1965) the child was seen as a young scientist who is testing hypotheses about the grammar of their language, based on the innate knowledge about possible structures of human languages. Later on (Chomsky, 1981), this view was changed to a process of maturation that involves the setting

of (innate) parameters based on the pld. In this view, the universal grammar was seen as a set of actual grammatical principles, and the differences between languages only arise by different setting of defined variables (e.g. Null-Subject-Parameter). A major adaptation of this framework came in 2002, when Hauser, Chomsky and Fitch proposed a distinction between a faculty of language in a broad sense, containing abilities shared with other cognitive domains, and in a narrow sense, containing only (very few) language specific functions (Hauser et al., 2002; cf. section 3.4.7).

While from a generativist viewpoint, language is seen as an organ in a biological sense that is encoded by the genes (Chomsky, 2000; Hauser et al., 2002), according to functionalist approaches, „cognitive processes involved in language are intimately related with its communicative and social interaction functions“ (Nadal et al., 2006, p. 188), excluding any specifically linguistic innate principles. Here, language is acquired by means of certain general learning mechanisms.

One argument for a global empiricism has been the cultural variability within the human race, where environment is thought to shape the mind, while biology only "imposes few constraints on our mental development" (Samuels, 2009). Moreover, according to Bates et al. (1998), strong nativists would have to assume representational nativism, i.e. that the innate knowledge must lie in the microcircuitry of the brain (Pinker, 1994). This possibility is often rebutted referring to the fact that the human genome only consists of about 24 000 genes, which could not predetermine the billions of connections between neurons in the brain (cf. Marcus, 2004; Samuels, 2009). These concerns, however, would also hold true for other, almost equally complex organs, and could only be used against a radically nativist view, in which all connections between individual neurons are genetically predetermined, while the interactionist thesis that cognitive development depends on both innate and environmental factors seems to be widely accepted to date (Marcus, 2004).

According to Bates (1994), three „logically separable issues“ are often connected and confused in the debate about the nature and evolution of human language: innateness, localization and domain specificity. Proponents of domain speci-

ficity state that language abilities, in addition to innate and localized, are „discontinuous from the rest of the mind" and „dissociable from all other perceptual and cognitive systems" (Bates, 1994, p. 136). Bates wonders whether it would be conceivable that "the brain of the newborn child [could] contain neural structures that are destined to mediate language, and language alone" (Bates, 1994, p. 136). Although language has to be innate „at some level of analysis", Bates doubts the mental organ claim. She favors a different approach in which language is seen as an „innate system, but one that involves a reconfiguration of mental and neural systems that exist in other species, and which continue to serve at least some non-linguistic functions in our own" (Bates, 1994, p. 136). As pointed out above (and discussed in detail in section 3.4.7) also the Chomskyan framework seems to converge on a similar position or at least not exclude anymore that the fraction of human language competence that is truly species and domain-specific is very limited if at all present (Hauser et al., 2002; Fitch et al., 2005).

Following Elman et al. (1998), Bates et al. (1998) propose an alternative to the traditional views of what is innate. As language is a product of a biological system and therefore is dependent on this hardware, the authors define constraints that are innate in the sense that they are based on the biological hardware:

- Representational constraints: corresponding to the underlying neuronal wiring
- Architectural constraints: Here, three sublevels are distinguished:
  - Basic computing parameters: neuron type, firing threshold, neurotransmitter, excitatory/inhibitory properties
  - Local architecture: number and thickness of layers, density of different cell types
  - Global architecture: characteristic sources of input and patterns of output, connections between brain regions
- Chronotopic constraints: timing of developmental events, spatio temporal waves of synaptic growth and cell division.

Bates et al. (1998) see this constraints-model as an alternative to extreme nativist views where everything is considered to be prewired. There have been also other attempts to avoid a strict dualism of innate vs. acquired traits. In a mathematical model of language acquisition across the human population, Kirby et al. (2007) extend the nature-nurture dualism to incorporate a third system that shapes language: culture. Although an implicit part of all not strictly nativist theories, culture is treated here as a separate factor in the ontogenesis as well as phylogenesis of a language. Cultural transmission, in their model, bridges the gap between the prior basis laid out by the genes and the language universals. The output of one learner becomes the input for the next generation in a process called iterated learning. With no other factors, even a small innate bias would always lead to the same outcome, and this does not fit with the existing variety of natural languages. In this model, genes constitute a fundamental, innate bias on the acquisition of a particular language, but the actual universal structure is heavily influenced by the interaction of speakers, with learning being "only part of the mechanism linking genes and the languages spoken in human societies" (Kirby et al., 2007, p. 5241). Cultural transmission involving iterated learning on the

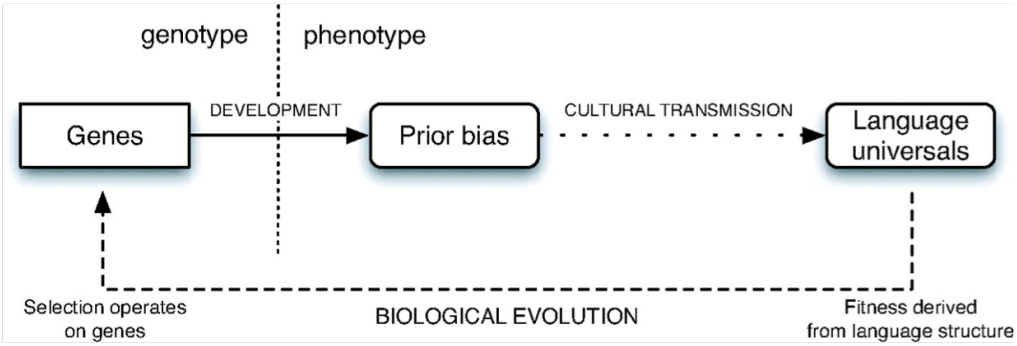

Figure 3.1: Cultural transmission, e.g. in the form of iterated learning, acts on a genetically encoded bias for the acquisition and evolution of a language, accounting for the manifold variations in the language structure that emerge from a similar biological endowment. Biological fitness is governed by the final language structure on a population-wide level and can influence biological evolution e.g. by selective pressure acting on genetic mutations (from Kirby et al., 2007, Fig. 2).

population level heavily influences the emergence of a language based on innate genetic biases (Fig. 3.1). These predispositions are also not unchangeable: "genes may code for the strength of a learning bias, but fitness and hence selection of those genes is determinded by the extended phenotype: in this case the properties of languages that emerge in populations" (Kirby et al., 2007, p. 5244). The authors argue, that „taking the role of culture into account provides alternative explanations for phenomena that might otherwise require an explanation in terms of innate biases or biological evolution" (p. 5244).

In contrast to the debates on what aspect of language and its acquisition is governed by biological endowment, environmental input and cultural transmission, respectively, developmental systems theories claim that innate and acquired aspects cannot be separated because they are intricately interlinked parts of a complex system guiding human behavior (cf. Tucic, 2002). Along similar lines, Bates et al. (1998) state that today the only reasonable answer to the nature-nurture controversy is, that "genes and environment interact to determine complex cognitive outcomes" (p. 590). Godfrey-Smith (2007) also stresses the inseparability of genetic and environmental factors in this context and points out that the relationship between the biological basis, i.e. the genes, and the trait under investigation, i.e. language, is not necessarily a direct, straightforward one, and that a link between a genetic program and a trait does not necessarily imply a causative relationship. Godfrey-Smith (2007) points out that genetically coded is not synonymous with genetically caused or genetically determined. Simple yes-no distinctions can only be made concerning the question if something is genetically coded, but this does not necessarily mean that this "coding" is reliably expressed. This decision can be affected by the environment, and a potential "natural connection between some genes and some traits [...] can be used to underwrite innateness claims" (p. 60). One example for such a connection is the relationship between DNA and the encoded protein: yes-or-no distinctions are possible for the case if one protein can be the product of a given DNA stretch. According to Godfrey-Smith, this is where the special "coding-for" relationship ends, but actually also much of the future life of this protein is predetermined by the DNA sequence (e.g. where in the cell it will be present and active). Godfrey-Smith is undoubtedly right, however, when

he states that there is a "crucial difference between the idea that genes code for proteins and genes code for whole-organism traits" (p. 62). Consequently Godfrey-Smith advises against a teleosemantic view on genes which assumes that genes have evolved to serve a particular function within an organism-level network and reflect the whole-organism phenotype.

Although it will not be able to maintain some extreme nativist positions in the light of new findings in biology, the rise of cognitivism has opened the door for a more balanced view, where both genetic and environmental factors are taken into consideration, and to a new popularity for speculations about the origin and foundation of human language (Tucic, 2002).

3.4 Common arguments for the innateness of language

Many arguments have been used in the discussion about the innateness of language, and some of the most common ones will be discussed in the following.

3.4.1 Universality

„The language faculty is universal, given that all healthy humans develop it, and specific because it is exclusive of the human species." (Nadal et al., 2006, p. 189)

The existence of linguistic universals, i.e. universal principles common to all languages such as the distinction between verbs and nouns, has been used as an argument for the innateness of language (e.g. Chomsky, 1988; Pinker, 1994). If there are universal principles of language that are the same, no matter how different the language superficially might be, then this argues for an innate set of rules common to all speakers of a human language. The main weakness of this argument, however, lies in the fact that it is very hard to determine what a true universal and its exact definition is. The first question is whether there are any truly

universal principles, since, as Samuels (2009) points out, "many proposed universals turn out on further scrutiny not to be possessed by all natural languages" (p. 328). This might also be a matter of interpretation, e.g. of grammatical categories, which may vary depending on the theoretical framework applied, as Tomasello (1995) stresses by postulating that there are „no theory-neutral structures in linguistics, and thus universality is a totally theory-dependent phenomenon" (p. 138). The validity of this argument also depends on the way human languages evolved. If all human languages spoken today derive from a common ur-language, then common principles in all present languages could just be explained historically by a common „ancestor language", without invoking an innate language faculty storing these principles (Bates, 1994; Tomasello, 1995). The same applies if these universals turn out to be very minimalistic and maybe just consequences of a common environment and shared needs and motivations of all speakers. In addition, as Samuels (2009) mentions, universals could be shaped by the characteristic principles of human thought, memory or our general capacity for symbolic communication (Tomasello, 2003).

A fundamental methodological problem is pointed out by Ariew (1999) who states that, if a trait is invariantly present in all individuals, there could be two reasons for that: either the trait is insensitive to environmental factors and in this sense innate, or the environmental conditions are invariably the same in respect to the relevant factors.

The genetic basis of language is almost exclusively universal, in that basically every human has the same set of genes, with the exception of some genetic variability. These small differences in the DNA sequence might very well have an influence on the individual's language competence, and in pathological cases (like the KE family and related cases presented earlier) severely impair language use.

3.4.2 Species specificity

If language is specific to humans then there might be some specific innate predisposition. While it is true that language in its human form is not found in any other

species, individual aspects are shared with the communication systems in other animals. This might even be true for components like recursion that are often considered to be exclusive to human language (Hauser et al., 2002). Considering the origin of language, Cowie (2010) hypothesizes that if language has emerged several times independently and yet complies with the same principles, this would strengthen the idea of an innate contribution to language competence. In the case of a specific innate predisposition, this would only hold true if the innate contribution that arose at that point was also (by chance) the same.

The fact that only humans use a communication system of this complexity does not prove that it is innate, as Tomasello (1995) points out. He mentions the fact that humans are also presumably the only species that cooks their food, yet there is probably no gene for cooking food. Although this is undeniably true, it is not really an argument against innateness in a reasonable way, since something can easily be innate without depending on a single gene.

Based on the fact that no neural structure, neuron type or neurotransmitter has been found so far that is unique to humans, Bates et al. (1998) advocate a view of quantitative (e.g. enlargement of certain brain regions), rather than qualitative differences that account for the human endowment to use language. Species-specific abilities could be an unintended by-product of a more general increase in computing power of the brain. The proposal by Hauser, Chomsky and Fitch (2002) that the specificity of the language faculty could be a result of the combination of traits not exclusive to humans also leaves the possibility open, that there does not need to be something fundamentally new at the biological level in order to give rise to a new (or at least immensely improved) skill at the cognitive level. Research on FOXP2 as a potential language gene has gone into a similar direction: Here the presence and functional similarity of this gene in most species and the comparatively small human-specific differences in the DNA sequence point also at a gradual improvement of existing principles rather than the emergence of something completely new, although small genetic differences can very well have widespread effects on the phenotypic level.

3.4.3 Localization of language competence in the brain

As discussed before (section 1.2), language use is related to activation of certain brain areas and lesions in language relevant cortical and subcortical regions lead to more or less predictable impairments, providing a link between a cognitive function and its biological hardware. Although it is certainly the case that some areas play an important role in language abilities, more and more data point at the interconnectedness of many brain regions for the performance of a given task. Moreover, although there is undoubtedly an innate predisposition of humans to use language, this does not imply anything about individual theory-specific principles being encoded in the genes of a newborn.

Historically, arguments for the existence of a specific neural substrate for language have been based on early research on aphasia localizing the motor aspects of language in Broca's area and the sensory functions in Wernicke's area. In the following, many researchers assumed the existence of innate, domain-specific and localized modules for grammar and semantics, while more recently the notion prevails that linguistic knowledge is broadly distributed in the adult brain, with some areas playing a more important role, and the information and its processing is not strictly localized (Bates, 1994).

According to Bates et al. (1998), „all knowledge presupposes localization in some form (compact and local, or broadly distributed)“ (p. 58), implying that localization per se is not a proof for innateness. Conversely, they state that if a cognitive ability is innate, it does not have to be „realized in some topographically specifiable way“ although „claims about innateness do presuppose a physical base”, which is why „cortical plasticity is so devastating to representational nativism“ (p. 58).

The expression and spatio-temporal activity pattern of FOXP2 can be seen as in accordance with a view of FOXP2 as a prerequisite for human language abilities. Human and mouse data indicate that this gene is involved in the formation of the same structures (notably the inferior frontal cortex and the basal ganglia) that are also thought to be centers of language processing in the brain. Although at this point, the data concerning the localization of language in the brain and the

expression pattern of FOXP2 is purely correlative, the possibility exists that future research will be able to identify a direct functional connection.

3.4.4 Existence of critical periods for the acquisition of language.

„In some instances, it occurs that organisms that are predetermined to manifest a specific trait – such as language in humans, according to Chomskyan theses – require the exposure to certain kinds of pertinent stimulation or experiences during a lapse of time which is also predetermined as critical“ (Nadal, 2006, p. 189).

Language acquisition is thought to be subject to temporal constraints, in that the child has to receive linguistic stimuli at a defined period during its development in order to reach full language competence (Lenneberg, 1967). The reason for the existence of critical periods might lie in physiological changes in the brain (Pinker, 1994).

In general, temporal restriction on the acquisition of certain abilities can be seen as genetically encoded or at least as a consequence of the developmental program of the organism (which in itself is then determined by the genes), when e.g. a certain external cue has to occur while a certain biological predisposition in the form of the expression of a certain set of genes is present. At this point it is unclear whether FOXP2, being a transcription factor and as such able to turn on and off a large set of genes, can be the key to a gene expression program that could provide the biological basis for the ability to acquire certain aspects of language at a certain time point.

3.4.5 Poverty of the stimulus – paradox of language acquisition

The most often cited argument for an innate knowledge of language deals with the primary linguistic data (pld), the input based on which the child acquires its

language competence. These pld are – according to Chomsky (1957) – „highly impoverished“, as

- they constitute a finite sample of the infinite number of sentences in a natural language
- they might not contain the kinds of sentences needed to falsify incorrect hypotheses during language acquisition.

This argument, known as Poverty of the Stimulus, is not necessarily restricted to language acquisition alone. Any input will necessarily be finite, and the learner has to be able to extract regularities that allow them to apply these rules to novel occurances, and thus „underdetermination of theories by their evidence [...] per se cannot be taken to be evidence for nativism“ (Cowie, 2010).

In his book „The Language Instinct“, Steven Pinker (1994) cites empirical studies showing that some errors that could be thought of as logical mistakes of someone acquiring a language just do not occur in the utterances of children. One example deals with the acquisition of auxiliaries (Stromswold, 1990). Here, Stromswold reports that children do not make the same mistakes (e.g. overgeneralizations like *doed*instead of *did*) for auxiliaries as for homophonous main verbs, indicating an ability to distinguish between these two groups at a very early stage of language acquisition, when much of the syntactic knowledge that by definition is needed to distinguish these two groups of verbs has not been acquired yet. Based on the developmental timing, the arbitrary behavior of auxiliaries and the lack of phonological distinctions to the corresponding main verb, Stromswold (and Pinker) argue that “children must be innately endowed with knowledge that makes it possible for them to distinguish main verbs from auxiliary verbs” (Stromswold, 1990, p. 265).

Nadal and colleagues (2006) call observations like this the paradox of language acquisition: children acquire the principles of language very early and in a fast and effortless way, largely irrespective of intelligence and environmental differences and in spite of incomplete and sometimes erroneous evidence (Chomsky, 1957; Chomsky, 1965; Chomsky, 1986).

The question of innateness and learnability is based on Gold's theorem (Gold, 1967) stating that grammars of this kind cannot be learned or guessed based on a finite number of positive examples in the absence of abundant negative evidence (which is thought to be the case for children acquiring language) or strong innate biases. According to Bates et al. (1998), this only applies „if we make assumptions about the learning device that are wildly unlike any known nervous system“ (p. 599). More recent mathematical simulations of language acquisition can be viewed as proof of learnability (cf. Elman et al., 1998). According to Bates (1994), a new era began with the work of Rummelhart and McClelland (1986), who showed that in a simulation on the acquisition of the English past tense, connectionist models predict similar stages like real language acquisition, e.g. overgeneralizations like comed and wented, that are replaced by the correct lexicalized forms without negative evidence. It might therefore be possible that the ability to acquire language is not as paradox as previously thought, and that what looks like specific patterns of defects (e.g. upon brain lesions) can in fact be due to damage or limitations in a general-purpose learning device (Bates, 1994).

3.4.6 The unlearning problem

In addition to the potential insufficiency of the input based on which the child has to infer the grammatical rules of the language, this input – according to many theorists – also lacks sufficient negative evidence to reject or modulate a wrong hypothesis (Cowie, 2010). The child could formulate – based on the pld it receives – a generalized rule that could explain all instances of a grammatical category, but would also be applied in cases where it leads to ungrammatical utterances. In the case of English past tense the child might generalize that for every verb the past tense is formed by adding the suffix -ed and has to learn that **I breaked it*is not a sentence of English. Negative evidence to reject the general applicability of this way of forming the past tense is not present in the pld, since there is no indication of explicit negative feedback (Marcus, 1993) and the pld „is mostly just a sample of sentences of positive instances of the target language“ (Cowie, 2010). There is no information about strings of words that do not form a grammatical sentence and the

child is also usually not corrected if it produces an ungrammatical sentence (Brown & Hanlon, 1970). According to linguistic nativists it is the universal grammar that provides restrictions for the necessary generalizations during the process of language acquisition.

In contrast to invoking an "innate" solution, Cowie (2010) argues that hypotheses do not necessarily need to be explicitly falsified in order to be rejected; lack of positive confirmation could be enough. In addition, rejection or modulation of a hypothesis might not necessarily involve negative data or explicit correction by speakers of the language, but negative evidence such as failure of the hearer to understand the child's utterances. Therefore, although explicit correction by the mother might not be common, „differential feedback" depending on how well formed the child's utterance was could serve a similar function.

Samuels (2009) mentions that the classical assumption that children do not encounter negative evidence has recently been doubted (e.g. Chouinard & Clark, 2003). Instead, research on statistical learning, i.e. making judgments based on frequency of occurrence, has presented this as a tool for the child to falsify hypotheses about their grammar (Pereira, 2000; Scholz & Pullum, 2006).

3.4.7 Modularity – cognitive specificity

The fact that language (and even subcomponents of it) seems to be – at least to some extent – physically separated from other cognitive functions and that it can be selectively affected (or spared) by brain damage has also been used as an argument for the innateness of language (cf. Cowie, 2010). Although no specific connections can be drawn between e.g. a universal linguistic principle and a neuronal circuit encoding this information, the fact that on a broader level some modularity and cognitive specificity of language seems to exist has led nativists to propose that the same also holds true on the level of individual linguistic concepts and that the basic neuronal structures and connectivity does not have to be established by learning but is innate.

With the increasing knowledge about the functioning of the brain, this argument is becoming weaker and weaker. Especially the immense plasticity of the brain and its ability to adjust to new situations (e.g. by rewiring or using certain brain areas to take over the function of other, maybe lesioned ones) suggests that even if there is a commonly used architecture of the language system in the brain, it can be modulated and new language areas can form in an experience-dependent process. This has been observed in several situations: not only is a lot of the visual cortex used for processing of Braille in congenitally blind subjects (Sadato et al., 1996), but also late-onset blindness leads to rewiring of the cortex for other perceptual tasks (Kujala et al., 1997). The same altered architecture can be observed for the auditory cortex in congenitally deaf persons, where brain areas that would normally be part of the auditory cortex are used for the processing of sign language (Nishimura et al., 1999).

The status of language as a specific cognitive module depends on the definition of a module. According to Bates (1994) this term has been used by neuroscientists and behavioral scientists in different ways. The first usually use this expression to refer to the anatomical structure of the brain and its organization in "cells, columns, layers and/or regions that divide up the labor of information processing in a variety of ways" (Bates, 1994, p. 137), but these processing units "are not complex faculties of mind, but elementary operations. More elaborate faculties are constructed from the serial and parallel (distributed) interconnections of several brain regions" (Kandel et al., 1991, p. 15). Behavioral scientists usually speak of modules as functional units, and Fodor (1983) lists nine criteria required for the classification as a module in this sense: Five of these describe how information is processed in a module and also hold true for acquired skills that function almost automatically.

- encapsulation (referring to the fact that it is not possible to interfere with the inner workings of a module)
- unconsciousness
- speed (fast processing)

- shallow outputs (the output of a module is limited, providing no information about the intervening steps)
- obligatory firing of the neurons involved (like a reflex).

Three more characteristics are then used to distinguish innate modules from learned habits:

- ontogenetic universals (modules develop in a characteristic sequence)
- localization (there are neural systems dedicated to these modules)
- pathological universals (modules break down in a characteristic way)

In addition, also domain specificity is seen as a requirement for a module, implying that they „deal with a single information type, albeit one of enormous relevance to the species" (Bates, 1994, p. 138).

In Fodor's view of a module, innateness, localization and domain specificity are combined, but all logical combinations of these three features are possible. Bates (1994) argues against a conflation of these criteria and her discussion of the extensive requirements for a module ends with the following (rhetorical) questions: "Have we evolved new neural tissue, a new region or a special form of comutation that deals with language, and language alone? And is that new mechanism guaranteed by its own special stretch of DNA?" (Bates, 1994, p. 140). Consequently she denies the domain specificity of language and lists arguments against it:

- phylogenetic recency: Given the estimates for the emergence of language, there would not be enough time to develop an innate system in the same way as for dealing with environmental factors like light and gravity.
- behavioral plasticity: despite all similarity, there is „surprising variability in structure and function across natural languages" (Bates, 1994, p. 141), much greater than for other putatively innate and domain-specific systems. According to Bates, learned proficiency in sign language argues strongly against domain specificity, but hints at an urge to communicate our thoughts and the existence of a set of information processing mechanisms.

- neural plasticity: Following early focal brain lesions, children develop normal language competence due to reorganization within the brain. This high degree of flexibility is not observed in other cognitive domains.

- arbitrariness of form-meaning mapping: while usually, in innate domain-specific knowledge, „there is always some kind of a physical constant, a partial isomorphism between the source of information in the world to which the animal must respond, and the internal state that the animal must take“ (p. 143), this is not the case for language.

- typical and atypical language development: As demonstrated by Petitto and Marentette (1991), deaf infants exposed to sign language babble with their hands, and the authors take this as evidence for innate abilites, which are independent of modality (vocal and manual), but specific to language. Bates agrees with the first, but not the second conclusion because children imitate novel actions at 8-10 months and the same happens in the case of the systematic input of sign language from the parents, so there is a general ability for imitation, which is not specific to language, but might be particularly well developed in humans.

All the research done in recent years on the functioning of the human brain and the cognitive abilities of other animals has led to a refinement of the view of a language module. Hauser, Chomsky and Fitch (2002) propose to distinguish between a faculty of language in the broad sense (FLB) and in the narrow sense (FLN). In this view, FLB would comprise several subcomponents like a sensory-motor and a conceptual-intentional system, among many others (cf. Fig. 3.2). These aspects would in general be shared with other species and with other psychological abilities, although they might be more developed in humans. The only truly human-specific components of language are – following the proposal of Hauser et al. (2002) – located in FLN. Although Hauser, Chomsky and Fitch leave some options open for other aspects to be added to the list, they assume that the computational mechanism of recursion is the only species-specific component of language. Surprisingly, they also entertain the idea that FLN might actually be completely empty (in case future research will show that recursion – in this sense – is also found in other

species), which would suggest that there is actually no aspect of language that is entirely specific to humans, but that the fact that enables humans to use a language of this complexity is the specific combination of modules (in FLB) that individually are also present in other species (Fitch et al., 2005).

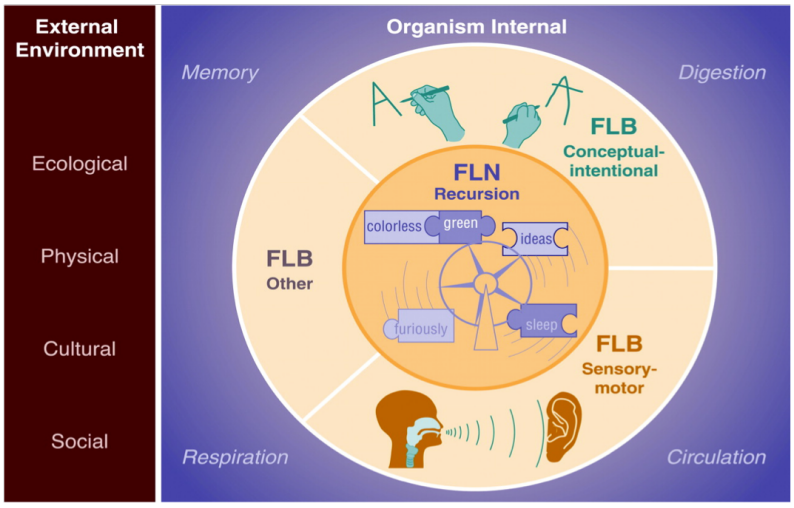

Figure 3.2: The organization of the language faculty according to Hauser et al. (2002): Most of the functions associated with language including the interfaces to other domains are localized in the broad faculty of language (FLB), while recursion as the presumably only aspect specific to language is found in the narrow faculty of language (FLN) (taken from Hauser et al., 2002, Fig. 2).

This model can be seen as a major adaptation of Chomsky's earlier view on the specificity of the language faculty as a mental organ, when he stated that "it would be surprising indeed if we were to find that the principles governing [linguistic] phenomena are operative in other cognitive systems" (Chomsky, 1980, p. 44). In the view put forth by Hauser et al. (2002), however, it seems like "very little is special to language, and that the special bits are minor modifications of other cognitive processes" (Pinker & Jackendoff, 2005, p. 204). In their critic of the proposal put forth by Hauser, Chomsky and Fitch, Pinker and Jackendoff (2005) doubt that everything apart from recursion should be excluded from the FLN (and hence be seen as not specific to language). They try to find an explanation of this model (and the apparent differences to Chomskys earlier views) in the minimal-

ist program, which aims at eliminating everything from a theory of language that is not truly indispensable. Apart from representations of sound and meaning the only other component that is absolutely necessary would therefore be an operation that combines individual units to form a hierarchical structure, Merge. Pinker and Jackendoff (2005) state that the "minimalist commitment to bare necessity leads to the conjecture that Merge is the onlyelement necessary to create the system of language" (p. 219). They in particular propose to include the capacity of vocal imitation in the domain-specific properties of language, since "humans are not notably talented at vocal imitation in general" (p. 209). In addition, also in the case of speech production they argue that the control of the speech apparatus in humans is "incomparably more complex" (Pinker & Jackendoff, 2005, p. 217), suggesting positive selection and evolution in the human lineage. Apart from the anatomical level, they also criticize the impact of Hauser, Chomsky and Fitch's proposal on language evolution. The existence of a minimalistic human-specific component would imply that only the ability for recursion was added "onto unchanged primate input-output abilities" (p. 218). Pinker and Jackendoff see the fact that there are multiple genetic loci, including FOXP2, associated with language impairments, but that none of these would compromise recursion selectively, as evidence for more than one language specific feature. Given the pleiotropic functions of FOXP2 and its presence in most species, Fitch, Hauser and Chomsky (2005) state that "[i]f anything is a candidate for inclusion in FLB but notin FLN, it is the FOXP2 gene" (p. 190). In their reply to the criticizm of the recursion-only view, Fitch, Hauser and Chomsky argue that FLN might very well contain additional modules, but in the case of vocal imitation this does not seem to be a likely scenario, given the apparent presence of this ability in non-human species. According to Fitch, Hauser and Chomsky (2005) a more plausible candidate for inclusion in FLN would instead be a language-specific word learning mechanism.

In terms of its evolution, Pinker and Jackendoff (2005) see language as "an adaptation for the communication of knowledge and intentions" (p. 231). While agreeing with this view on the level of many of the subsystems of language, Fitch, Hauser and Chomsky (2005) warn to treat language as a "monolithic whole" for which a "single adaptive function" (p. 189) could be identified. They also raise

doubts about the specific evolution of language modules for communicative purposes, following earlier opinions that the need to communicate alone would not create a selective pressure strong enough to push the evolution of language in its entirety (Luria, 1974). Focusing on language in the narrow sense of Hauser et al. (2002), Pinker and Jackendoff (2005) correctly conclude that "[i]f language per se does not consist of very much, then not much had to evolve for us to get it" (p.219). In this case even a single genetic change could have been enough. Nevertheless, Hauser, Chomsky and Fitch (2002) propose that even FLN (and in particular recursion) might not have evolved for the use in communication, but might have been adapted later on, when its initial purpose became obsolete giving humans the possibility, "perhaps uniquely, to apply the power of recursion to other problems" (p. 1578).

In the case of FLB, Fitch, Hauser and Chomsky (2005) agree with Pinker and Jackendoff that these abilities have been adapted for the purpose of communication. The fact that FLB can be fractionated into individual components on the one hand opens the possibility that each of these has a different history of evolution and adaptation to language. On the other hand, the non-domain-specific nature of these components opens the possibility of investigating each of them individually at multiple levels ("mechanistic, developmental, phylogenetic and functional" (Fitch et al., 2005, p189)). This also makes it possible to study these mechanisms in other contexts and adapt the conclusions to language, thereby advancing biolinguistics as an empirical science. On the other hand, this view of the language faculty might lead to the identification of some aspects that have been traditionally studied by linguists in a language-specific manner, but may actually represent consequences of computational or other constraints, which lie outside of FLN and therefore cannot be expected to be attributable to linguistic reasons (alone) (Hauser et al., 2002).

3.4.8 Pidgins and creoles

„Creolization typically occurs when migrant workers who speak a variety of languages are brought together to work and their only common language is a simplified

version of the dominant language, known as a pidgin. Pidgins typically consist of fixed phrases and pantomimes and can be used to express only basic needs and ideas“ (Ganger & Stromswold, 1998, p. 201).

Derek Bickerton (1981) observed that the creolized language of second-generation pidgin speakers is much more complex than the pidgin input they received. According to Ganger and Stromswold (1998) „studies of creolization thus provide compelling evidence that human children are programmed to develop a specific kind of language even with minimal input“ (p. 201). In the case of deaf children of hearing parents that are not exposed to sign language, these children receive no language input at all. If this does not happen until puberty, they do not develop normal language skills. Also in this scenario, however, the initial steps and trials to find a language are the same as in children exposed to normal pld (Goldin-Meadow & Mylander, 1984), suggesting an innate program of language acquisition.

This last example already suggests that the basis for innate linguistic universals is encoded in the genome, and many researchers have more specifically addressed this question.

3.4.9 Genetic studies

Evidence based on genetics influences the discussion of many arguments for innateness, but genetic studies have also been used and cited more directly to prove the nativist's point. A prerequisite for evolution by natural selection is the existence of genetic variation in a species, so “[i]f we can discover genetic variation in language in modern humans, we may gain insight into the genetic variation that was relevant in the evolution of language“ (Ganger & Stromswold, 1998, p. 208). In addition, this naturally occurring variation can also be informative in a synchronous perspective, if it were possible to correlate certain changes at the DNA level with the performance in language tasks. In general, genetic similarity seems to allow predictions about linguistic abilities, since comparisons of adopted children with their biological and adopted family members indicated that “genetic factors play a greater role than environmental factors in language abilities” (Ganger &

Stromswold, 1998, p. 210). Another example comes from the aforementioned twin studies, which in general show a higher concordance in language deficits (or language competence in general) between monozygotic versus dizygotic twins (Gibson & Gruen, 2008; Hayiou-Thomas, 2008).

With the exception of these cases, correlations of language competence and genotype have, up to now, been mainly carried out for more extreme cases of language proficiency (Williams syndrome) or specific impairment (SLI, Down syndrome), and these examples are continuously cited as arguments in favor of an innate, separate language faculty (cf. Bartke & Siegmüller, 2004). Some researchers, however, see these as "further evidence for the behavioral and neural plasticity of language" (Bates, 1994, p. 147) rather than as support for a mental organ view of language competence. Bates et al. (1998) raise concerns that these observations are being misinterpreted as pointing at a specific link between a genetic locus and language competence or even a particular grammatical operation, stating that these disorders might not be as specific to language processing as initially hoped and that, conversely, deficits specific to language might also not be innate "in any interesting sense". Based on

- the occurrence of certain morphological deficits (e.g. loss of the ability for tense marking) following very diverse forms of brain damage,
- on the fact that problems in hearing alone also preferentially lead to defects in morphological marking and
- on studies showing that also unaffected subjects make similar mistakes if they have to carry out a linguistic task while being distracted or asked to perform a competing task at the same time,

Bates et al. (1998) conclude that "[g]rammatical morphemes tend to be low in perceptual salience and imageability, and perhaps for this reason, they constitute a 'weak link in the processing chain'" (p. 596).

This view might challenge the importance of studies on SLI, Williams or Down syndrome for questions of innateness and domain specificity, but the two positions are not mutually exclusive. In contrast, it seems almost intuitive that the "costs" in

terms of memory capacity for a task like the processing of morphological markers come from the activation of many different brain regions that have to act together, potentially in a specific manner that is unlike the processing mechanisms for other tasks, but will still rely on the same, potentially limiting, processes of working memory, lexical retrieval and coordination of motor outputs.

3.5 Conclusions

Although there is widespread agreement that the human ability to use language is innate "at some level" and therefore must have a genetic representation, views differ considerably when it comes to how much and what is innate. While representational nativism, i.e. the existence of a defined physical counterpart of every linguistic item and grammatical process, seems to be clearly falsified by the evidence available to date, it is still unclear if there are higher order organizational units in the brain dedicated specifically to language, or if language uses the same mechanisms that are also utilized for other cognitive tasks. Bates, for example, argues for the latter view, in which language is innate, but not domain-specific, relying on a plastic mix of neural systems that also serve other functions, which „renders the mysteries of language evolution [...] more tractable. That is, the continuities that we have observed between language and other cognitive systems make it easier to see how this capacity came about in the first place" (Bates, 1994, p. 149).

Along similar lines, Hauser, Chomsky and Fitch (2002) propose that most aspects of language are not domain-specific. In contrast to Bates, however, they still leave space for a language-specific component like recursion. For other researchers (e.g. Pinker & Jackendoff, 2005) this domain-specific contribution is too minor and they propose that a larger part of language processing might have evolved for and be used specifically by linguistic tasks.

An alternative to a simple distinction between innate and acquired knowledge is put forward by Bates et al. (1998) who, instead of invoking innate representations of linguistic concepts, explain language acquisition and processing by "architectural and temporal constraints that require much less genetically specified information"

(Bates et al., 1998, p. 599), providing an emergentist solution to the nature vs. nurture controversy. Samuels (2009) also emphasizes that all models assume some language-specific constraints, e.g. on the input the child receives. This might lead to a variant of linguistic nativism: one that posits an innate, language-specific statistical learning mechanism or module.

Although the question how much of linguistic knowledge is innate at a conceptual level and the quest for genes underlying human language competence are intricately connected, the explanatory potential that one aspect can have on the other is naturally limited. An innate trait can be expected to have a genetic foundation, but as long as there are several structural and functional levels in between that are unresolved, no strong conclusions can be made concerning a functionally specific relation between a gene and language competence. Genetic information and behavioral output constitute the two extremes on the biological landscape, and progress in knowledge about the link of these two points necessarily has to be made in a step-wise fashion from both sides. The function of a gene has to be clarified, especially in terms of potential tissue specificity in expression and functioning, before strong conclusions can be made concerning its role on the tissue level. On the other hand, the macroscopic processing of language in the brain has to be exhaustively elucidated, before conclusions about the individual contributions of certain brain areas or cell clusters are justified. As long as the gap between these two levels has not been closed, a link between a gene and its function in language processing in the brain can only be speculative. In this sense, and based on the evidence available to date, we are still far from identifying the genetic component (which will be most likely more complex than a single "language gene") enabling humans to speak. On the other hand, even an incomplete and in the end potentially unjustifiably strong link between a gene and a cognitive function can advance our understanding of the highly complex system governing the emergence of a speaking individual based on the information stored in its genome and might reveal new genetic features contributing to the linguistic abilities specific to humans.

Bibliography

Abrahams BS, Tentler D, Perederiy JV, Oldham MC, Coppola G, Geschwind DH (2007) Genome-wide analyses of human perisylvian cerebral cortical patterning. *Proc Natl Acad Sci U S A* **104**(45)**:** 17849-17854.

Ackermann H (2008) Cerebellar contributions to speech production and speech perception: psycholinguistic and neurobiological perspectives. *Trends in Neurosciences* **31**(6): 265-272.

Alarcon M, Abrahams BS, Stone JL, Duvall JA, Perederiy JV, Bomar JM, Sebat J, Wigler M, Martin CL, Ledbetter DH, Nelson SF, Cantor RM, Geschwind DH (2008) Linkage, association, and gene-expression analyses identify CNTNAP2 as an autism-susceptibility gene. *Am J Hum Genet* **82**(1)**:** 150-159.

Alcock KJ, Passingham RE, Watkins KE, Vargha-Khadem F (2000) Oral dyspraxia in inherited speech and language impairment and acquired dysphasia. *Brain Lang* **75**(1)**:** 17-33.

Anderson SR, Lightfoot DW (2002) *The Language Organ: Linguistics as Cognitive Physiology*, Cambridge: Cambridge University Press.

Ariew A (1996) Innateness and Canalization. *Philosophy of Science* **63:** S19-S27.

Ariew A (1999) Innateness is Canalization: In Defense of a Developmental Account of Innateness. In *Where Biology Meets Psychology: Philosophical Essays*, Hardcastle VG (ed), pp 117-138. Cambridge, MA: MIT Press.

Bartke S, Siegmüller J (eds) (2004) *Williams Syndrome across Languages*. Amsterdam: John Benjamins.

Bartlett CW, Flax JF, Logue MW, Vieland VJ, Bassett AS, Tallal P, Brzustowicz LM (2002) A major susceptibility locus for specific language impairment is located on 13q21. *Am J Hum Genet* **71**(1)**:** 45-55.

Basso A, Capitani E, Laiacona M, Zanobio ME (1985) Crossed aphasia: one or more syndromes? *Cortex* **21**(1)**:** 25-45.

Bates E (1994) Modularity, domain specificity and the development of language. In *Evolution and Neurology of Language. Discussions in Neuroscience*, Gajdusek DC, McKhann GM, Bolis CL (eds), Vol. 10, pp 136-149. Amsterdam: Elsevier.

Bates E, Elman J, Johnson M, Karmiloff-Smith A, Parisi D, Plunkett K (1998) Innateness and Emergentism. In *A companion to cognitive science*, Bechtel W, Graham G (eds), pp 590-601. Oxford: Basil Blackwell.

Bateson P (1991) Are there principles of behavioural development? In *The Development and Integration of Behaviour*, Bateson P (ed), pp 19-39. Cambridge: Cambridge University Press.

Bel-Vialar S, Itasaki N, Krumlauf R (2002) Initiating Hox gene expression: in the early chick neural tube differential sensitivity to FGF and RA signaling subdivides the HoxB genes in two distinct groups. *Development* **129**(22)**:** 5103-5115.

Belton E, Salmond CH, Watkins KE, Vargha-Khadem F, Gadian DG (2003) Bilateral brain abnormalities associated with dominantly inherited verbal and orofacial dyspraxia. *Hum Brain Mapp* **18**(3)**:** 194-200.

Bickerton D (1981) *Roots of Language*, Ann Arbor: Karoma.

Bickerton D (2007) Language evolution: A brief guide for linguists. *Lingua* **117:** 510-526.

Bishop DV (2009) Genes, cognition, and communication: insights from neurodevelopmental disorders. *Ann N Y Acad Sci* **1156:** 1-18.

Bishop DV, North T, Donlan C (1995) Genetic basis of specific language impairment: evidence from a twin study. *Dev Med Child Neurol* **37**(1)**:** 56-71.

Bishop DVM (2006) What causes specific language impairment in children? *Curr Dir Psychol Sci* **15**(5)**:** 217-221.

Broca P (1861) Nouvelle observation produite par une lésion de la troisième circonvolution frontale. *Bulletins de la Société d'anatomie* **6:** 398-407.

Brown R, Hanlon C (1970) Derivational complexity and order of acquisition in child speech. In *Cognition and the development of language*, Hayes JR (ed), pp 155-207. New York: Wiley.

Brown WM (2011) The parental antagonism theory of language evolution: preliminary evidence for the proposal. *Hum Biol* **83**(2)**:** 213-245.

Busslinger M (2004) Transcriptional control of early B cell development. *Annu Rev Immunol* **22:** 55-79.

Campbell P, Reep RL, Stoll ML, Ophir AG, Phelps SM (2009) Conservation and diversity of Foxp2 expression in muroid rodents: functional implications. *J Comp Neurol* **512**(1)**:** 84-100.

Caplan D, Utman JA (1994) Selective acoustic phonetic impairment and lexical access in an aphasic patient. *J Acoust Soc Am* **95**(1)**:** 512-517.

Caplan D, Waters G, DeDe G, Michaud J, Reddy A (2004) A study of syntactic processing in aphasia I: Behavioral (psycholinguistic) aspects. *Brain and Language* **91**(1)**:** 64-65.

Carlsson P, Mahlapuu M (2002) Forkhead transcription factors: key players in development and metabolism. *Dev Biol* **250**(1)**:** 1-23.

Chomsky N (1957) *Syntactic structures*, The Hague/Paris: Mouton.

Chomsky N (1959) A Review of B. F. Skinner's Verbal Behavior. *Language* **35**(1)**:** 26-58.

Chomsky N (1965) *Aspects of the theory of syntax*, 2. print. edn. Cambridge, Mass.: MIT Press.

Chomsky N (1980) *Rules and representations*, New York: Columbia Univ. Press.

Chomsky N (1981) *Lectures on government and binding*, Dordrecht: Foris Publ.

Chomsky N (1986) *Knowledge of language, its nature, origin, and use*, 6. print. edn. New York, NY: Praeger.

Chomsky N (1988) *Language and problems of knowledge, the Managua lectures*, Cambridge, MA: MIT Press.

Chomsky N (1995) *The minimalist program*, Cambridge, MA: MIT Press.

Chomsky N (2000) *New horizons in the study of language and mind*, 1. publ. edn. Cambridge: Cambridge Univ. Press.

Chouinard MM, Clark EV (2003) Adult reformulations of child errors as negative evidence. *J Child Lang* **30**(3)**:** 637-669.

Coop G, Bullaughey K, Luca F, Przeworski M (2008) The timing of selection at the human FOXP2 gene. *Mol Biol Evol* **25**(7)**:** 1257-1259.

Cooper DL (2006) Broca's arrow: evolution, prediction, and language in the brain. *Anat Rec B New Anat* **289**(1)**:** 9-24.

Cope N, Harold D, Hill G, Moskvina V, Stevenson J, Holmans P, Owen MJ, O'Donovan MC, Williams J (2005) Strong evidence that KIAA0319 on chromosome 6p is a susceptibility gene for developmental dyslexia. *Am J Hum Genet* **76**(4)**:** 581-591.

Cowie F (1999) *What's Within? Nativism Reconsidered*, Oxford: Oxford University Press.

Cowie F (2009) Why Isn't Stich an Eliminativist? In *Stich and His Critics*, Murphy D, Bishop MA (eds), pp 74-100. Wiley-Blackwell.

Cowie F. (2010) Innateness and Language. In *The Stanford Encyclopedia of Philosophy (Summer 2010 edition)*, Zalta EN (ed.), http://plato.stanford.edu/entries/innateness-language/, accessed 20.2.2013.

Critchley M (1979) Diagnosis of dyslexia. *J R Soc Med* **72**(7)**:** 542.

Cullicover P, Jackendoff R (2005) *Simpler Syntax*, Oxford: Oxford University Press.

DeFries JC, Fulker DW, LaBuda MC (1987) Evidence for a genetic aetiology in reading disability of twins. *Nature* **329**(6139)**:** 537-539.

Di Sciullo AM, Piatelli-Palmarini M, Wexler K, Berwick RC, Boeckx C, Jenkins L, Uriagereka J, Stromswold K, Cheng LL, Harley H, Wedel A, McGilvray J, van Gelderen E, Bever TG (2010) The Biological Nature of Human Language. *Biolinguistics* **4**(1)**:** 4-34.

Dominguez MH, Rakic P (2009) Language evolution: The importance of being human. *Nature* **462**(7270)**:** 169-170.

Dronkers NF, Redfern BB, Knight RT (2000) The neural architecture of language disorders. In *The New Cognitive Neurosciences*, Gazzaniga MS (ed), pp 949-958. Cambridge, MA: The MIT Press.

Elman J, Bates E, Johnson M, Karmiloff-Smith A, Parisi D, Plunkett K (1998) *Rethinking innateness: A connectionist perspective on development*, Cambridge, MA: MIT Press.

Enard W, Przeworski M, Fisher SE, Lai CS, Wiebe V, Kitano T, Monaco AP, Paabo S (2002) Molecular evolution of FOXP2, a gene involved in speech and language. *Nature* **418**(6900)**:** 869-872.

Enard W, Gehre S, Hammerschmidt K, Holter SM, Blass T, Somel M, Brueckner MK, Schreiweis C, Winter C, Sohr R, Becker L, Wiebe V, Nickel B, Giger T, Muller U, Groszer M, Adler T, Aguilar A, Bolle I, Calzada-Wack J, Dalke C, Ehrhardt N, Favor J, Fuchs H, Gailus-Durner V, Hans W, Holzlwimmer G, Javaheri A, Kalaydjiev S, Kallnik M, Kling E, Kunder S, Mossbrugger I, Naton B, Racz I, Rathkolb B, Rozman J, Schrewe A, Busch DH, Graw J, Ivandic B, Klingenspor M, Klopstock T, Ollert M, Quintanilla-Martinez L, Schulz H, Wolf E, Wurst W, Zimmer A, Fisher SE, Morgenstern R, Arendt T, de Angelis MH, Fischer J, Schwarz J, Paabo S (2009) A humanized version of Foxp2 affects cortico-basal ganglia circuits in mice. *Cell* **137**(5)**:** 961-971.

Enard W (2011) FOXP2 and the role of cortico-basal ganglia circuits in speech and language evolution. *Curr Opin Neurobiol* **21**(3)**:** 415-424.

Farrer L (2004) Collection of clinical and epidemiological data for linkage studies. *Curr Protoc Hum Genet* **Chapter 1:** Unit 1.1.

Ferland RJ, Cherry TJ, Preware PO, Morrisey EE, Walsh CA (2003) Characterization of Foxp2 and Foxp1 mRNA and protein in the developing and mature brain. *J Comp Neurol* **460**(2)**:** 266-279.

Fischer J, Hammerschmidt K (2011) Ultrasonic vocalizations in mouse models for speech and socio-cognitive disorders: insights into the evolution of vocal communication. *Genes Brain Behav* **10**(1)**:** 17-27.

Fisher SE, Scharff C (2009) FOXP2 as a molecular window into speech and language. *Trends Genet* **25**(4)**:** 166-177.

Fisher SE, Vargha-Khadem F, Watkins KE, Monaco AP, Pembrey ME (1998) Localisation of a gene implicated in a severe speech and language disorder. *Nat Genet* **18**(2)**:** 168-170.

Fitch WT, Hauser MD, Chomsky N (2005) The evolution of the language faculty: clarifications and implications. *Cognition* **97**(2)**:** 179-210.

Fletcher P (1990) Speech and language defects. *Nature* **346:** 226.

Fodor JA (1983) *The modularity of mind: an essay on faculty psychology*, Cambridge, MA: MIT Press.

Francis F, Koulakoff A, Boucher D, Chafey P, Schaar B, Vinet MC, Friocourt G, McDonnell N, Reiner O, Kahn A, McConnell SK, Berwald-Netter Y, Denoulet P, Chelly J (1999) Doublecortin is a developmentally regulated, microtubule-associated protein expressed in migrating and differentiating neurons. *Neuron* **23**(2)**:** 247-256.

Friedman JI, Vrijenhoek T, Markx S, Janssen IM, van der Vliet WA, Faas BH, Knoers NV, Cahn W, Kahn RS, Edelmann L, Davis KL, Silverman JM, Brunner HG, van Kessel AG, Wijmenga C, Ophoff RA, Veltman JA (2008) CNTNAP2 gene dosage variation is associated with schizophrenia and epilepsy. *Mol Psychiatry* **13**(3)**:** 261-266.

Friederici AD (2002) Towards a neural basis of auditory sentence processing. *Trends in Cognitive Science* **6**(2)**:** 78-84.

Friederici AD (2006) The neural basis of language development and its impairment. *Neuron* **52**(6)**:** 941-952.

Fujita E, Tanabe Y, Shiota A, Ueda M, Suwa K, Momoi MY, Momoi T (2008) Ultrasonic vocalization impairment of Foxp2 (R552H) knockin mice related to speech-language disorder and abnormality of Purkinje cells. *Proc Natl Acad Sci U S A* **105**(8)**:** 3117-3122.

Fukuchi-Shimogori T, Grove EA (2001) Neocortex patterning by the secreted signaling molecule FGF8. *Science* **294**(5544)**:** 1071-1074.

Galaburda AM, Sherman GF, Rosen GD, Aboitiz F, Geschwind N (1985) Developmental dyslexia: four consecutive patients with cortical anomalies. *Ann Neurol* **18**(2)**:** 222-233.

Gall FJ (1798) Schreiben über seinen bereits geendigten Prodromus über die Verrichtungen des Gehirns der Menschen und der Thiere an Herrn Jos. Fr. von Retzer. *Der neue Teutsche Merkur* **3**: 311-332.

Ganger J, Stromswold K (1998) Innateness, evolution, and genetics of language. *Hum Biol* **70**(2)**:** 199-213.

Gathercole SE (2006) Nonword repetition and word learning: The nature of the relationship. *Applied Psycholinguistics* **27**(4)**:** 513-543.

Gaub S, Groszer M, Fisher SE, Ehret G (2010) The structure of innate vocalizations in Foxp2-deficient mouse pups. *Genes Brain Behav* **9**(4)**:** 390-401.

Geschwind N (1967) The varieties of naming errors. *Cortex* **3:** 97-112.

Geschwind N, Levitsky W (1968) Left-right asymmetries in temporal speech region. *Science* **161:** 186-187.

Geschwind N, Quadfasel FA, Segarra JM (1968) Isolation of the speech area. *Neuropsychologia* **6**(4)**:** 327-340.

Gibson CJ, Gruen JR (2008) The human lexinome: genes of language and reading. *J Commun Disord* **41**(5)**:** 409-420.

Godfrey-Smith P (2007) Innateness and Genetic Information. In *The Innate Mind, Volume 3: Foundations and the Future*, Carruthers P, Lawrence S, Stich S (eds), pp 55-68. Oxford: Oxford University Press.

Gold EM (1967) Language identification in the limit. *Information and Control* **16:** 447-474.

Goldin-Meadow S, Mylander C (1984) Gestural communication in deaf children: the effects and noneffects of parental input on early language development. *Monogr Soc Res Child Dev* **49**(3-4)**:** 1-151.

Gopnik M (1990) Feature-blind grammar and dysphagia. *Nature* **344**(6268)**:** 715.

Gopnik M (1997) Language deficits and genetic factors. *Trends in Cognitive Sciences* **1**(1)**:** 5-9.

Gopnik M, Crago MB (1991) Familial aggregation of a developmental language disorder. *Cognition* **39**(1)**:** 1-50.

Graham SA, Fisher SE (2013) Decoding the genetics of speech and language. *Curr Opin Neurobiol* **23**(1)**:** 43-51.

Gray PA, Fu H, Luo P, Zhao Q, Yu J, Ferrari A, Tenzen T, Yuk DI, Tsung EF, Cai Z, Alberta JA, Cheng LP, Liu Y, Stenman JM, Valerius MT, Billings N, Kim HA, Greenberg ME, McMahon AP, Rowitch DH, Stiles CD, Ma Q (2004) Mouse brain organization revealed through direct genome-scale TF expression analysis. *Science* **306**(5705)**:** 2255-2257.

Griffiths PE (1997) *What Emotions Really Are: The Problem of Psychological Categories.*, Chicago: University of Chicago Press.

Griffiths PE (2002) What Is Innateness? *Monist* **85**(1)**:** 70-85.

Griffiths R (1970) *The abilities of young children*, London: Child Development Research Centre.

Grigorenko EL (2003) The first candidate gene for dyslexia: Turning the page of a new chapter of research. *Proc Natl Acad Sci U S A* **100**(20)**:** 11190-11192.

Grodzinsky Y (2006) The language faculty, Broca's region, and the mirror system. *Cortex* **42**(4)**:** 464-468.

Grodzinsky Y, Friederici AD (2006) Neuroimaging of syntax and syntactic processing. *Curr Opin Neurobiol* **16**(2)**:** 240-246.

Groszer M, Keays DA, Deacon RM, de Bono JP, Prasad-Mulcare S, Gaub S, Baum MG, French CA, Nicod J, Coventry JA, Enard W, Fray M, Brown SD, Nolan PM, Paabo S, Channon KM, Costa RM, Eilers J, Ehret G, Rawlins JN, Fisher SE (2008) Impaired synaptic plasticity and motor learning in mice with a point mutation implicated in human speech deficits. *Curr Biol* **18**(5)**:** 354-362.

Habib M (2000) The neurological basis of developmental dyslexia: an overview and working hypothesis. *Brain* **123 Pt 12:** 2373-2399.

Haesler S, Wada K, Nshdejan A, Morrisey EE, Lints T, Jarvis ED, Scharff C (2004) FoxP2 expression in avian vocal learners and non-learners. *J Neurosci* **24**(13)**:** 3164-3175.

Haesler S, Rochefort C, Georgi B, Licznerski P, Osten P, Scharff C (2007) Incomplete and inaccurate vocal imitation after knockdown of FoxP2 in songbird basal ganglia nucleus Area X. *PLoS Biol* **5**(12)**:** e321.

Hagoort P (2006) On Broca, Brain and Binding. In *Broca's Region*, Grodzinsky Y, Amunts K (eds). Oxford: Oxford University Press.

Hanahan D, Weinberg RA (2000) The hallmarks of cancer. *Cell* **100**(1)**:** 57-70.

Hannula-Jouppi K, Kaminen-Ahola N, Taipale M, Eklund R, Nopola-Hemmi J, Kaariainen H, Kere J (2005) The axon guidance receptor gene ROBO1 is a candidate gene for developmental dyslexia. *PLoS Genet* **1**(4)**:** e50.

Hasson U, Small SL (2008) Functional Magnetic Resonance Imaging (fMRI) Research of Language. In *Handbook of the Neuroscience of Language*, Stemmer B, Whitaker HA (eds), pp 81-90. London/Amsterdam/Burlington, MA/San Diego, CA: Academic Press.

Hauser MD, Chomsky N, Fitch WT (2002) The faculty of language: what is it, who has it, and how did it evolve? *Science* **298**(5598)**:** 1569-1579.

Hayiou-Thomas ME (2008) Genetic and environmental influences on early speech, language and literacy development. *J Commun Disord* **41**(5)**:** 397-408.

Hirshorn EA, Thompson-Schill SL (2006) Role of the left inferior frontal gyrus in covert word retrieval: neural correlates of switching during verbal fluency. *Neuropsychologia* **44**(12)**:** 2547-2557.

Horwitz B, Wise RJS (2008) PET Research of Language. In *Handbook of the Neuroscience of Language*, Stemmer B, Whitaker HA (eds), pp 71-80. London/Amsterdam/Burlington, MA/San Diego, CA: Academic Press.

Hurst JA, Baraitser M, Auger E, Graham F, Norell S (1990) An extended family with a dominantly inherited speech disorder. *Dev Med Child Neurol* **32**(4)**:** 352-355.

Indefrey P, Levelt WJ (2004) The spatial and temporal signatures of word production components. *Cognition* **92**(1-2)**:** 101-144.

Jackendoff R (1994) *Patterns in the Mind: Language and Human Nature*, New York: Basic Books.

Jakubowicz C (2003) Computational complexity and the acquisition of functional categories by French-speaking children with SLI. *Linguistics* **41:** 175-211.

Kandel ER, Schwartz JHS, Jessell TM (1991) *Principles of Neural Science*, 3rd edn. Norwalk, CT: Appleton & Lange.

Kehayia E (1994) Whole-word access or decomposition in word recognition in Familial Language Impairment: A psycholinguistic study. *McGill Working Papers in Linguistics* **10:** 123-128.

Kehayia E (1997) Lexical access and representation in individuals with developmental language impairment: A cross-linguistic study. *Journal of Neurolinguistics* **10**(2-3)**:** 139-149.

Kirby S, Dowman M, Griffiths TL (2007) Innateness and culture in the evolution of language. *Proc Natl Acad Sci U S A* **104**(12)**:** 5241-5245.

Knoblich JA (1997) Mechanisms of asymmetric cell division during animal development. *Curr Opin Cell Biol* **9**(6)**:** 833-841.

Konopka G, Bomar JM, Winden K, Coppola G, Jonsson ZO, Gao F, Peng S, Preuss TM, Wohlschlegel JA, Geschwind DH (2009) Human-specific transcriptional regulation of CNS development genes by FOXP2. *Nature* **462**(7270)**:** 213-217.

Krause J, Lalueza-Fox C, Orlando L, Enard W, Green RE, Burbano HA, Hublin JJ, Hanni C, Fortea J, de la Rasilla M, Bertranpetit J, Rosas A, Paabo S (2007) The derived FOXP2 variant of modern humans was shared with Neandertals. *Curr Biol* **17**(21)**:** 1908-1912.

Kujala T, Alho K, Huotilainen M, Ilmoniemi RJ, Lehtokoski A, Leinonen A, Rinne T, Salonen O, Sinkkonen J, Standertskjold-Nordenstam CG, Naatanen R (1997) Electrophysiological evidence for cross-modal plasticity in humans with early- and late-onset blindness. *Psychophysiology* **34**(2)**:** 213-216.

Lai CS, Fisher SE, Hurst JA, Levy ER, Hodgson S, Fox M, Jeremiah S, Povey S, Jamison DC, Green ED, Vargha-Khadem F, Monaco AP (2000) The SPCH1 region on human 7q31: genomic characterization of the critical interval and localization of translocations associated with speech and language disorder. Am J Hum Genet 67(2): 357-368.

Lai CS, Fisher SE, Hurst JA, Vargha-Khadem F, Monaco AP (2001) A forkhead-domain gene is mutated in a severe speech and language disorder. Nature 413(6855): 519-523.

Lai CS, Gerrelli D, Monaco AP, Fisher SE, Copp AJ (2003) FOXP2 expression during brain development coincides with adult sites of pathology in a severe speech and language disorder. Brain 126(Pt 11): 2455-2462.

Lander ES, Linton LM, Birren B, Nusbaum C, Zody MC, Baldwin J, Devon K, Dewar K, Doyle M, FitzHugh W, Funke R, Gage D, Harris K, Heaford A, Howland J, Kann L, Lehoczky J, LeVine R, McEwan P, McKernan K, Meldrim J, Mesirov JP, Miranda C, Morris W, Naylor J, Raymond C, Rosetti M, Santos R, Sheridan A, Sougnez C, Stange-Thomann N, Stojanovic N, Subramanian A, Wyman D, Rogers J, Sulston J, Ainscough R, Beck S, Bentley D, Burton J, Clee C, Carter N, Coulson A, Deadman R, Deloukas P, Dunham A, Dunham I, Durbin R, French L, Grafham D, Gregory S, Hubbard T, Humphray S, Hunt A, Jones M, Lloyd C, McMurray A, Matthews L, Mercer S, Milne S, Mullikin JC, Mungall A, Plumb R, Ross M, Shownkeen R, Sims S, Waterston RH, Wilson RK, Hillier LW, McPherson JD, Marra MA, Mardis ER, Fulton LA, Chinwalla AT, Pepin KH, Gish WR, Chissoe SL, Wendl MC, Delehaunty KD, Miner TL, Delehaunty A, Kramer JB, Cook LL, Fulton RS, Johnson DL, Minx PJ, Clifton SW, Hawkins T, Branscomb E, Predki P, Richardson P, Wenning S, Slezak T, Doggett N, Cheng JF, Olsen A, Lucas S, Elkin C, Uberbacher E, Frazier M, Gibbs RA, Muzny DM, Scherer SE, Bouck JB, Sodergren EJ, Worley KC, Rives CM, Gorrell JH, Metzker ML, Naylor SL, Kucherlapati RS, Nelson DL, Weinstock GM, Sakaki Y, Fujiyama A, Hattori M, Yada T, Toyoda A, Itoh T, Kawagoe C, Watanabe H, Totoki Y, Taylor T, Weissenbach J, Heilig R, Saurin W, Artiguenave F, Brottier P, Bruls T, Pelletier E, Robert C, Wincker P, Smith DR, Doucette-Stamm L, Rubenfield M, Weinstock K, Lee HM, Dubois J, Rosenthal A, Platzer M, Nyakatura G, Taudien S, Rump A, Yang H, Yu J, Wang J, Huang G, Gu J, Hood L, Rowen L, Madan A, Qin S, Davis RW, Federspiel NA, Abola AP, Proctor MJ, Myers RM, Schmutz J, Dickson M, Grimwood J, Cox DR, Olson MV, Kaul R, Shimizu N, Kawasaki K, Minoshima S, Evans GA, Athanasiou M, Schultz R, Roe BA, Chen F, Pan H, Ramser J, Lehrach H, Reinhardt R, McCombie WR, de la Bastide M, Dedhia N, Blocker H, Hornischer K, Nordsiek G, Agarwala R, Aravind L, Bailey JA, Bateman A, Batzoglou S, Birney E, Bork P, Brown DG, Burge CB, Cerutti L, Chen HC, Church D, Clamp M, Copley RR, Doerks T, Eddy SR, Eichler EE, Furey TS, Galagan J, Gilbert JG, Harmon C,

Hayashizaki Y, Haussler D, Hermjakob H, Hokamp K, Jang W, Johnson LS, Jones TA, Kasif S, Kaspryzk A, Kennedy S, Kent WJ, Kitts P, Koonin EV, Korf I, Kulp D, Lancet D, Lowe TM, McLysaght A, Mikkelsen T, Moran JV, Mulder N, Pollara VJ, Ponting CP, Schuler G, Schultz J, Slater G, Smit AF, Stupka E, Szustakowski J, Thierry-Mieg D, Thierry-Mieg J, Wagner L, Wallis J, Wheeler R, Williams A, Wolf YI, Wolfe KH, Yang SP, Yeh RF, Collins F, Guyer MS, Peterson J, Felsenfeld A, Wetterstrand KA, Patrinos A, Morgan MJ, de Jong P, Catanese JJ, Osoegawa K, Shizuya H, Choi S, Chen YJ (2001) Initial sequencing and analysis of the human genome. *Nature* **409**(6822)**:** 860-921.

Laws G, Bishop DV (2004) Verbal deficits in Down's syndrome and specific language impairment: a comparison. *Int J Lang Commun Disord* **39**(4)**:** 423-451.

Lee A, Kannan V, Hillis AE (2006) The contribution of neuroimaging to the study of language and aphasia. *Neuropsychol Rev* **16**(4)**:** 171-183.

Lenneberg EH (1967) *Biological Foundations of Language*, New York: Wiley.

Leonard L (1998) *Children with Specific Language Impairement*, Cambridge, MA: MIT Press.

Lewis BA (1992) Pedigree Analysis of Children with Phonology Disorders *J Learning Disabilities* **25:** 586-597.

Libben G (2005) Brain and Language. In *Contemporary Linguistic Analysis*, Archibald J, O'Grady W (eds), 5th edn, pp 473-493. Toronto, ON: Copp Clark Pitman Ltd.

Lichtheim L (1885) Über Aphasie. *Deutsches Archiv für klinische Medicin* **36:** 204-268.

Lieberman P (2006) *Toward an evolutionary biology of language*, Cambridge, MA: Harvard University Press.

Lieberman P (2009) FOXP2 and Human Cognition. *Cell* **137**(5)**:** 800-802.

Liegeois F, Baldeweg T, Connelly A, Gadian DG, Mishkin M, Vargha-Khadem F (2003) Language fMRI abnormalities associated with FOXP2 gene mutation. *Nat Neurosci* **6**(11)**:** 1230-1237.

Luria S (1974) Comments. In: *A Debate on Bio-Linguistics*, Piattelli-Palmarini M (ed.). MIT and Centre Royaumont Pour une Science de l'homme.

MacDermot KD, Bonora E, Sykes N, Coupe AM, Lai CS, Vernes SC, Vargha-Khadem F, McKenzie F, Smith RL, Monaco AP, Fisher SE (2005) Identification of FOXP2 truncation as a novel cause of developmental speech and language deficits. *Am J Hum Genet* **76**(6)**:** 1074-1080.

Mameli M, Bateson P (1996) Innateness and the Sciences. *Biology and Philosophy* **21:** 155-188.

Marcus G (2004) *The Birth of the Mind*, New York: Basic Books.

Marcus GF (1993) Negative evidence in language acquisition. *Cognition* **46**(1)**:** 53-85.

Marcus GF, Fisher SE (2003) FOXP2 in focus: what can genes tell us about speech and language? *Trends Cogn Sci* **7**(6)**:** 257-262.

Marinis T (2011) On the nature and cause of Specific Language Impairment: A view from sentence processing and infant research. *Lingua* **121**(3)**:** 463-475.

Marsden CD, Obeso JA (1994) The functions of the basal ganglia and the paradox of stereotaxic surgery in Parkinson's disease. *Brain* **117**(Pt 4)**:** 877-897.

Meng H, Smith SD, Hager K, Held M, Liu J, Olson RK, Pennington BF, DeFries JC, Gelernter J, O'Reilly-Pol T, Somlo S, Skudlarski P, Shaywitz SE, Shaywitz BA, Marchione K, Wang Y, Paramasivam M, LoTurco JJ, Page GP, Gruen JR (2005) DCDC2 is associated with reading disability and modulates neuronal development in the brain. *Proc Natl Acad Sci U S A* **102**(47)**:** 17053-17058.

Middleton FA, Strick PL (2000) Basal ganglia and cerebellar loops: motor and cognitive circuits. *Brain Res Brain Res Rev* **31**(2-3)**:** 236-250.

Miller JE, Spiteri E, Condro MC, Dosumu-Johnson RT, Geschwind DH, White SA (2008) Birdsong decreases protein levels of FoxP2, a molecule required for human speech. *J Neurophysiol* **100**(4)**:** 2015-2025.

Nadal M, Amengual-Bunyola GA, Ramis C, Capo M, Cela Conde CJ (2006) Recent genetic contributions to the study of language. *Ludus Vitalis* **XIV**(25)**:** 187-204.

Nishimura DY, Searby CC, Alward WL, Walton D, Craig JE, Mackey DA, Kawase K, Kanis AB, Patil SR, Stone EM, Sheffield VC (2001) A spectrum of FOXC1 mutations suggests gene dosage as a mechanism for developmental defects of the anterior chamber of the eye. *Am J Hum Genet* **68**(2)**:** 364-372.

Nishimura H, Hashikawa K, Doi K, Iwaki T, Watanabe Y, Kusuoka H, Nishimura T, Kubo T (1999) Sign language 'heard' in the auditory cortex. *Nature* **397**(6715)**:** 116.

Obler LK, Gjerlow K (1999) *Language and the brain*, Cambridge, UK: Cambridge University Press.

Osborne LR, Mervis CB (2007) Rearrangements of the Williams-Beuren syndrome locus: molecular basis and implications for speech and language development. *Expert Rev Mol Med* **9**(15)**:**1-16.

Paracchini S, Thomas A, Castro S, Lai C, Paramasivam M, Wang Y, Keating BJ, Taylor JM, Hacking DF, Scerri T, Francks C, Richardson AJ, Wade-Martins R, Stein JF, Knight JC, Copp AJ, Loturco J, Monaco AP (2006) The chromosome 6p22 haplotype associated with dyslexia reduces the expression of KIAA0319, a novel gene involved in neuronal migration. *Hum Mol Genet* **15**(10)**:** 1659-1666.

Pauling L, Coryell CD (1936) The Magnetic Properties and Structure of Hemoglobin, Oxyhemoglobin and Carbonmonoxyhemoglobin. *Proc Natl Acad Sci U S A* **22**(4)**:** 210-216.

Pereira F (2000) Formal Grammar and Information Theory: Together Again? *Philosophical Transactions of the Royal Society* **A358:** 1239–1253.

Petitto LA, Marentette PF (1991) Babbling in the manual mode: evidence for the ontogeny of language. *Science* **251**(5000)**:** 1493-1496.

Pickett ER, Kuniholm E, Protopapas A, Friedman J, Lieberman P (1998) Selective speech motor, syntax and cognitive deficits associated with bilateral damage to the putamen and the head of the caudate nucleus: a case study. *Neuropsychologia* **36**(2)**:** 173-188.

Pinker S (1991) Rules of language. *Science* **253**(5019)**:** 530-535.

Pinker S (1994) *The language instinct: How the Mind Creates Language* New York City, NY.

Pinker S, Jackendoff R (2005) The faculty of language: what's special about it? *Cognition* **95**(2)**:** 201-236.

Plomin R, DeFries JC, McClearn GE, McGuffin P (2001) *Behavioral Genetics*, 4th ed. edn. New York: Worth Publishers.

Prince VE, Moens CB, Kimmel CB, Ho RK (1998) Zebrafish hox genes: expression in the hindbrain region of wild-type and mutants of the segmentation gene, valentino. *Development* **125**(3)**:** 393-406.

Pulvermüller F, Shtyrov Y, Hauk O (2009) Understanding in an instant: Neurophysiological evidence for mechanistic language circuits in the brain. *Brain and Language* **110**(2)**:** 81-94.

Ramus F (2006) Genes, brain, and cognition: a roadmap for the cognitive scientist. *Cognition* **101**(2)**:** 247-269.

Reimers-Kipping S, Hevers W, Paabo S, Enard W (2011) Humanized Foxp2 specifically affects cortico-basal ganglia circuits. *Neuroscience* **175:** 75-84.

Rodden FA, Stemmer B (2008) A Brief Introduction to Common Neuroimaging Techiques. In *Handbook of the Neuroscience of Language*, Stemmer B, Whitaker HA (eds), pp 57-70. London/Amsterdam/Burlington, MA/San Diego, CA: Academic Press.

Rumelhart D, McClelland J (1986) *Parallel distributed processing: Explorations in the microstructure of cognition*, Cambridge, MA: MIT Press.

Sadato N, Pascual-Leone A, Grafman J, Ibanez V, Deiber MP, Dold G, Hallett M (1996) Activation of the primary visual cortex by Braille reading in blind subjects. *Nature* **380**(6574)**:** 526-528.

Saleem RA, Banerjee-Basu S, Berry FB, Baxevanis AD, Walter MA (2003) Structural and functional analyses of disease-causing missense mutations in the forkhead domain of FOXC1. *Hum Mol Genet* **12**(22)**:** 2993-3005.

Samet J. (2008) The Historical Controversies Surrounding Innateness. In *The Stanford Encyclopedia of Philosophy (Fall 2008 edition)*, Zalta EN (ed.), http://plato.stanford.edu/entries/innateness-history/, accessed 20.2.2013.

Samples JM, Lane VW (1985) Genetic possibilities in six siblings with specific language learning disorders. *ASHA* **27**(12)**:** 27-32.

Samuels R (2002) Nativism in Cognitive Science. *Mind & Language* **17**(3)**:** 233-265.

Samuels R (2004) Innateness and Cognitive Science. *Trends in Cognitive Sciences* **8**(3), pp 136-141.

Samuels R (2009) Nativism. In The Routledge Companion to Philosophy of Psychology, Symons J, Calvo P (eds), pp 322-335. New York: Routledge.

Scharff C, Haesler S (2005) An evolutionary perspective on FoxP2: strictly for the birds? *Curr Opin Neurobiol* **15**(6)**:** 694-703.

Scharff C, Petri J (2011) Evo-devo, deep homology and FoxP2: implications for the evolution of speech and language. *Philos Trans R Soc Lond B Biol Sci* **366**(1574)**:** 2124-2140.

Scholz BC, Pullum GK (2006) Irrational Nativist Exuberance. In *Debates in Cognitive Science*, Stainton R (ed). Oxford: Blackwell.

Schulz SB, Haesler S, Scharff C, Rochefort C (2010) Knockdown of FoxP2 alters spine density in Area X of the zebra finch. *Genes Brain Behav* **9**(7)**:** 732-740.

Semendeferi K, Lu A, Schenker N, Damasio H (2002) Humans and great apes share a large frontal cortex. *Nat Neurosci* **5**(3)**:** 272-276.

Shalom DB, Poeppel D (2008) Functional anatomic models of language: assembling the pieces. *Neuroscientist* **14**(1)**:** 119-127.

Shu W, Yang H, Zhang L, Lu MM, Morrisey EE (2001) Characterization of a new subfamily of winged-helix/forkhead (Fox) genes that are expressed in the lung and act as transcriptional repressors. *J Biol Chem* **276**(29)**:** 27488-27497.

Shu W, Cho JY, Jiang Y, Zhang M, Weisz D, Elder GA, Schmeidler J, De Gasperi R, Sosa MA, Rabidou D, Santucci AC, Perl D, Morrisey E, Buxbaum JD (2005) Altered ultrasonic vocalization in mice with a disruption in the Foxp2 gene. *Proc Natl Acad Sci U S A* **102**(27)**:** 9643-9648.

Shu W, Lu MM, Zhang Y, Tucker PW, Zhou D, Morrisey EE (2007) Foxp2 and Foxp1 cooperatively regulate lung and esophagus development. *Development* **134**(10)**:** 1991-2000.

Skinner BF (1957) *Verbal behavior*, New York, NY: Appleton-Century-Crofts.

Spiteri E, Konopka G, Coppola G, Bomar J, Oldham M, Ou J, Vernes SC, Fisher SE, Ren B, Geschwind DH (2007) Identification of the transcriptional targets of FOXP2, a gene linked to speech and language, in developing human brain. *Am J Hum Genet* **81**(6)**:** 1144-1157.

Stich SP (1975) The idea of innateness. In *Innate Ideas*, Stich SP (ed). Los Angeles: University of California Press.

Stromswold K (1990) *Learnability and the acquisition of auxiliaries.* Unpublished doctoral dissertation, Massachusetts Institute of Technology, Cambridge, MA.

Takahashi K, Liu FC, Hirokawa K, Takahashi H (2003) Expression of Foxp2, a gene involved in speech and language, in the developing and adult striatum. *J Neurosci Res* **73**(1)**:** 61-72.

Taipale M, Kaminen N, Nopola-Hemmi J, Haltia T, Myllyluoma B, Lyytinen H, Muller K, Kaaranen M, Lindsberg PJ, Hannula-Jouppi K, Kere J (2003) A candidate gene for developmental dyslexia encodes a nuclear tetratricopeptide repeat domain protein dynamically regulated in brain. *Proc Natl Acad Sci U S A* **100**(20)**:** 11553-11558.

Takahashi K, Liu FC, Oishi T, Mori T, Higo N, Hayashi M, Hirokawa K, Takahashi H (2008) Expression of FOXP2 in the developing monkey forebrain: comparison with the expression of the genes FOXP1, PBX3, and MEIS2. *J Comp Neurol* **509**(2)**:** 180-189.

Tallal P, Ross R, Curtiss S (1989) Familial aggregation in specific language impairment. *Journal of Speech and Hearing Disorders* **54:** 167-173.

Teramitsu I, Kudo LC, London SE, Geschwind DH, White SA (2004) Parallel FoxP1 and FoxP2 expression in songbird and human brain predicts functional interaction. *J Neurosci* **24**(13)**:** 3152-3163.

Teramitsu I, White SA (2006) FoxP2 regulation during undirected singing in adult songbirds. *J Neurosci* **26**(28)**:** 7390-7394.

Teramitsu I, Poopatanapong A, Torrisi S, White SA (2010) Striatal FoxP2 is actively regulated during songbird sensorimotor learning. *PLoS One* **5**(1)**:** e8548.

Tomasello M (1995) Language is Not an Instinct. *Cognitive Development* **10:** 131-156.

Tomasello M (2003) *Constructing a Language: A Usage-Based Theory of Language Acquisition*, Cambridge, MA: Harvard University Press.

Tomblin JB, Records NL, Buckwalter P, Zhang X, Smith E, O'Brien M (1997) Prevalence of specific language impairment in kindergarten children. *J Speech Lang Hear Res* **40**(6)**:** 1245-1260.

Tranel D, Martin C, Damasio H, Grabowski TJ, Hichwa R (2005) Effects of noun-verb homonymy on the neural correlates of naming concrete entities and actions. *Brain Lang* **92**(3)**:** 288-299.

Trinkaus E (2007) Human Evolution: Neandertal gene speaks out. *Curr Biol* **17**(21)**:** R917-919.

Tucic N (2002) Genes, Humans and Society. *Genetika* **34**(2-3)**:** 97-100.

Ullman MT, Corkin S, Coppola M, Hickok G, Growdon JH, Koroshetz WJ, Pinker S (1997) A Neural Dissociation within Language: Evidence that the Mental Dictionary Is Part of Declarative Memory, and that Grammatical Rules Are Processed by the Procedural System. *Journal of Cognitive Neuroscience* **9**(2)**:** 266-276.

Ullman MT, Gopnik M (1999) Inflectional morphology in a family with inherited specific language impairment. *Applied Psycholinguistics* **20:** 51-117.

Ullman MT (2001) A neurocognitive perspective on language: the declarative/procedural model. *Nat Rev Neurosci* **2**(10)**:** 717-726.

Ullman MT, Pierpont EI (2005) Specific language impairment is not specific to language: the procedural deficit hypothesis. *Cortex* **41**(3)**:** 399-433.

Vallender EJ, Mekel-Bobrov N, Lahn BT (2008) Genetic basis of human brain evolution. *Trends Neurosci* **31**(12)**:** 637-644.

van der Lely HK, Rosen S, McClelland A (1998) Evidence for a grammar-specific deficit in children. *Curr Biol* **8**(23)**:** 1253-1258.

Vargha-Khadem F, Gadian DG, Copp A, Mishkin M (2005) FOXP2 and the neuroanatomy of speech and language. *Nat Rev Neurosci* **6**(2)**:** 131-138.

Vargha-Khadem F, Passingham RE (1990) Speech and language defects. *Nature* **346:** 226.

Vargha-Khadem F, Watkins K, Alcock K, Fletcher P, Passingham R (1995) Praxic and nonverbal cognitive deficits in a large family with a genetically transmitted speech and language disorder. *Proc Natl Acad Sci U S A* **92**(3)**:** 930-933.

Vargha-Khadem F, Watkins KE, Price CJ, Ashburner J, Alcock KJ, Connelly A, Frackowiak RS, Friston KJ, Pembrey ME, Mishkin M, Gadian DG, Passingham RE (1998) Neural basis of an inherited speech and language disorder. *Proc Natl Acad Sci U S A* **95**(21)**:** 12695-12700.

Vernes SC, Spiteri E, Nicod J, Groszer M, Taylor JM, Davies KE, Geschwind DH, Fisher SE (2007) High-throughput analysis of promoter occupancy reveals direct neural targets of FOXP2, a gene mutated in speech and language disorders. *Am J Hum Genet* **81**(6)**:** 1232-1250.

Vernes SC, Newbury DF, Abrahams BS, Winchester L, Nicod J, Groszer M, Alarcon M, Oliver PL, Davies KE, Geschwind DH, Monaco AP, Fisher SE (2008) A functional genetic link between distinct developmental language disorders. *N Engl J Med* **359**(22)**:** 2337-2345.

Vernes SC, Oliver PL, Spiteri E, Lockstone HE, Puliyadi R, Taylor JM, Ho J, Mombereau C, Brewer A, Lowy E, Nicod J, Groszer M, Baban D, Sahgal N, Cazier JB, Ragoussis J, Davies KE, Geschwind DH, Fisher SE (2011) Foxp2 regulates gene networks implicated in neurite outgrowth in the developing brain. *PLoS Genet* **7**(7)**:** e1002145.

Villanueva P, Newbury DF, Jara L, De Barbieri Z, Mirza G, Palomino HM, Fernandez MA, Cazier JB, Monaco AP, Palomino H (2011) Genome-wide analysis of genetic susceptibility to language impairment in an isolated Chilean population. *Eur J Hum Genet* **19**(6)**:** 687-695.

Waddington CH (1942) Canalization of development and the inheritance of acquired characters. *Nature* **150:** 563-565.

Wang Y, Paramasivam M, Thomas A, Bai J, Kaminen-Ahola N, Kere J, Voskuil J, Rosen GD, Galaburda AM, Loturco JJ (2006) DYX1C1 functions in neuronal migration in developing neocortex. *Neuroscience* **143**(2)**:** 515-522.

Watkins KE, Gadian DG, Vargha-Khadem F (1999) Functional and structural brain abnormalities associated with a genetic disorder of speech and language. *Am J Hum Genet* **65**(5)**:** 1215-1221.

Watkins KE, Dronkers NF, Vargha-Khadem F (2002) Behavioural analysis of an inherited speech and language disorder: comparison with acquired aphasia. *Brain* **125**(Pt 3)**:** 452-464.

Weaver TD, Roseman CC, Stringer CB (2008) Close correspondence between quantitative- and molecular-genetic divergence times for Neandertals and modern humans. *Proc Natl Acad Sci U S A* **105**(12)**:** 4645-4649.

Wernicke C (1874) *Der aphasische Symptomencomplex: eine psychologische Studie auf anatomischer Basis*, Breslau: M. Crohn und Weigert.

Wexler K (1998) Very early parameter setting and the unique checking constraint: A new explanation of the optional infinitive stage. *Lingua* **106:** 23-79.

White SA (2010) Genes and vocal learning. *Brain Lang* **115**(1)**:** 21-28.

Wimsatt WC (1986) Developmental Constraints, Generative Entrenchment and the Innate-Aquired Distinction. In *Integrating Scientific Disciplines*, Bechtel W (ed), pp 185-208. Dordrecht: Martinus Nijhoff.

Wimsatt WC (1999) Generativity, Entrenchment, Evolution, and Innateness: Philosophy, Evolutionary Biology, and Conceptual Foundations of Science. In *Where Biology Meets Psychology: Philosophical Essays*, Hardcastle VG (ed), pp 139-179. Cambridge, MA: MIT Press.

Zeigler HP, Marler P (2008) *The Neuroscience of Birdsong*, Cambridge: Cambridge University Press.

Abstract

Language, as a complex symbol system thought to be especially elaborate in humans, is necessarily built on a physical basis. The strongest and most apparent link exists between language and its biological „hardware“, and one aspect of this is the relationship between the genetic endowment and linguistic abilities. In this thesis, I try to outline the quest to identify individual genes necessary for human language ability and their respective functional contributions. One of the most prominent examples found so far is a gene called FOXP2, mutations in which have been identified as the cause of inherited language disorders. The product of this gene functions as a transcription factor, i.e. a protein regulating – positively or negatively – the expression of a large number of target genes, and changes in its activity can therefore have far reaching consequences.

In the last decade, a plethora of studies were conducted examining the functional role of FOXP2 and trying to shed light on its importance for human language skills. In parallel, speech deficits of affected patients were investigated and linguistic models of the role of this „language gene“ were proposed. The aim of this thesis is to bring both lines of research together and to attempt to evaluate investigations and models on an interdisciplinary basis and taking into account the findings from researchers of diverse backgrounds. Another aspect of FOXP2's status as a “language gene” is its presence in other species. Here, especially research on songbirds suggests an interesting, evolutionarily conserved function of FOXP2 as a prerequisite for vocal communication, with apparent species-specific differences.

The third part of this thesis is centered around the question, how biological evidence can be reconciled with linguistic theory, or in what respect it even corroborates the models. Especially in the debate about the innateness of human language abilities, introduced into linguistics with the rise of cognitivism, research on genes like FOXP2 could contribute to a better understanding and provide biologically substantiated linguistic arguments.

Zusammenfassung

Sprache als ein komplexes Zeichen- und Kommunikationssystem hat notwendigerweise eine physische Basis. Die stärkste und offensichtlichste Verbindung besteht hier zwischen Sprache und ihrer biologischen Grundlage, wobei ein Aspekt das Verhältnis zwischen der genetischen Information und den sprachlichen Fähigkeiten ist. Diese Arbeit soll einen Überblick bieten über die Bemühungen zur Identifizierung von einzelnen Genen, die notwendig für die menschliche Sprachfähigkeit sind, und zur Charakterisierung ihrer spezifischen Funktionen. Eines der bestuntersuchten Beispiele ist das FOXP2 Gen, bei welchem spezifische Mutationen als Ursache von sprachlichen Beeinträchtigungen identifiziert wurden. Das Produkt dieses Gens ist ein Transkriptionsfaktor, d.h. ein Protein, das die Expression von anderen Genen beeinflussen kann, sodass Veränderungen in seiner Aktivität weitreichende Konsequenzen haben können.

Im letzten Jahrzehnt wurde eine Vielzahl von Studien durchgeführt mit dem Ziel, die Funktion von FOXP2 und seine biologische Rolle in Bezug auf die menschliche Sprachfähigkeit zu definieren. Parallel dazu wurden die sprachlichen Defizite von Patienten mit FOXP2 Mutationen untersucht und linguistische Modelle für die Rolle dieses Gens formuliert. Das Ziel dieser Arbeit ist es, beide Forschungsrichtungen zusammenzuführen und die Ergebnisse und Modelle aus einer interdisziplinären Perspektive zu bewerten. Als weiterer Aspekt in der Untersuchung von FOXP2 als potenziellem Sprachgen wird auch die Funktion von FOXP2 in anderen Arten behandelt. In diesem Zusammenhang haben vor allem Erkenntnisse in Singvögeln eine neue Sichtweise auf FOXP2 als evolutionär weit verbreiteter Grundlage von Kommunikationssystemen gebracht, allerdings mit klaren gattungsspezifischen Charakteristika.

Der dritte Teil dieser Arbeit beschäftigt sich mit der Frage, wie neue biologische Erkenntnisse mit linguistischer Theorie in Einklang zu bringen sind oder in welcher Hinsicht sie vielleicht sogar die existierenden Modelle bestätigen. Vor allem in der Debatte um die Angeborenheit der menschlichen Sprachfähigkeit könnte die Forschung an Genen wie FOXP2 zu einem besseren Verständnis beitragen und biologisch fundierte Argumente für linguistische Theorien liefern.

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Tübing, F., G. Vendra, **M. Mikl**, Y. Xie, M. Zeitelhofer, R. Dahm, S. Thomas, P. Macchi and M. A. Kiebler (2010). "Microinjected RNAs are specifically sorted into dendrites of living hippocampal neurons." J Neurosci 30(11):4160-70.

Mikl, M., G. Vendra, M. Doyle and M. A. Kiebler (2010). "RNA localization in neurite morphogenesis: current evidence and novel approaches." Review, J Comp Physiol-A 196(5):321-34.

Mikl, M., G. Vendra and M. A. Kiebler (2011). "Independent localization of MAP2, CaMKIIα.and β-actin in low copy numbers". EMBO Rep 12(10):1077-84.

Presentations at meetings

Vendra, G.*, **M. Mikl***, F. Tuebing, K. Czaplinski and M.A. Kiebler, (* equal contribution), Poster presented at the FASEB RNA localization meeting, Vermont, USA, 2009.

M. Mikl, G. Vendra, F. Tuebing and M.A. Kiebler, "MAP2, CaMKIIa and beta-actin mRNAs localize to dendrites in disitinct RNPs in low copy numbers and are differentially regulated by Staufen2", Poster presented at the EMBO-ESF conference on RNA quality control, Vienna, Austria, 10-13 May, 2010.

M. Mikl and C.R. Cowan, "The splicing regulator SPK-1 is required for cell polarity establishment in the one-cell C. elegans embryo.", Poster presented at the EMBO C. elegans conference series: C. elegans development and gene expression, EMBL Heidelberg, Germany, 17-20 June, 2010.

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M. Mikl and C.R. Cowan, "The splicing regulator SPK-1 is required for cell polarity in one-cell C. elegans embryos.", Poster presented at the EMBO/EMBL symposium: The complex life of mRNA, EMBL, Heidelberg, 7-10 Oct, 2012.

M. Mikl and C.R. Cowan, "Alternative 3'UTR selection controls cell polarity in C. elegans embryos.", Podium Presentation at the Gordon Research Conference Developmental Biology, Barga, Lucca, Italy, 30 June – 5 July, 2013.

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