

# The effect of GABRB3 polymorphisms on brain function and structure in healthy male volunteers assessed by multimodal imaging

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## Appendix C

# Addendum of valorisation

### C.1 Relevance of the study

The study presented here must be judged in the context of the neuroimaging genetic studies, an emerging field with a great potential.

The study of heredity has brought numerous and great advances in the understanding and treatment of several pathological entities. This is valid not just for diseases that result from mutations, but also for diseases where the genetic predisposition plays an important role, such as the metabolic, neurological and psychiatric diseases. Interestingly, even the immunological responses during infectious diseases are known to be strongly determined by genetic factors. Nowadays, it is clear that heredity is involved in the development and course of a large number of entities affecting the human being. This dissertation is, therefore, a piece of scientific work focused on elucidating the mechanisms through which heredity influences the function and structure of the brain.

The brain is the most complex of all organs. Their individual cells are quite different from each other in their transcriptomes, proteomes, phenotypes and also in the thousands of connections and interactions. The neurogenetic studies have greatly contributed to the understanding of how the nervous system of individuals differ despite belonging to the same species, and how the structural differences influence traits in personality and define predisposition to diseases. Several of the inter-individual differences are not easily observable, and are difficult to measure and quantify. This is precisely the role of neuroimaging tools

in imaging genetic studies: to provide quantifiable and measurable features to make inferences about the variances observed.

Unquestionably, variations in the linear sequence of the genetic code play a key role in explaining inter-individual differences in structure and function of the brain, as well as give insight into susceptibility and resistance in a wide range of diseases. There is strong evidence that a number of psychiatric illnesses such as schizophrenia, bipolar disorder, autism, and alcoholism have a genetic basis. A number of neurologic diseases such as dementias, epilepsies, dystonias, Parkinsons disease, ataxias, polyneuropathies, dystrophies and phakomatoses have also been associated with genetic factors. This dissertation focused on the beta-3 subunit of the GABA type A receptors (GABRB3), which has associations with epileptic encephalopathies in humans, Angelman syndrome and autism. The case of epilepsy, for example, is particularly interesting, for the reason that it implies the failures of several regulatory systems. Alterations in the expression of the GABRB3 gene might affect the expression of the GABA type A receptors by altering receptor function and/or by impairing receptor biogenesis. Alterations in the expression of the beta-3 subunits might lead to several alterations: inhibition of receptor trafficking, reduction in the subunit mRNA transcription or stability, impairing subunit folding, stability, or oligomerization. Although the actual mechanisms must be elucidated, the results presented strongly suggest the existence of changes in the activity of both gene and receptor. This dissertation is, in this sense, putting the grounds for further studies.

This dissertation is an example of a neuroimaging genetic study, where a candidate gene is chosen and comparisons are performed on the basis of the most prevalent genetic variant in a population. The most prevalent genetic variant found in this study was the same one found in all populations studied thus far. Therefore, the results presented in this study have a great deal of importance for the general population. The results presented in the dissertation found, for the first time, the actual features where the expression of the GABRB3 gene influences brain structure. Therefore, this study is pioneer in using the GABRB3 gene as candidate gene in a neuroimaging genetics study. Interestingly, the results of the dissertation confirm the alterations found in Angelman syndrome. This was an un-expected outcome and opens the possibilities to assess progresses in an eventual genetic therapeutic approach targeting this rare disease. Moreover, the differences in slow-frequency EEG oscillations might also be of utility in the

follow-up of patients suffering from epilepsy caused by alterations in GABRB3 expression. For the causal diagnosis of epilepsy, the results found here would be of help in case of altered global delta voltage. Although more studies are needed, quantitative EEG might be used in the future as diagnostic tool, and might play an important role in the future of epilepsy treatment.

## C.2 Target groups

The diagnosis and treatment of epilepsy are a great deal in everyday medicine practice. About 2% of adults have a seizure at some time during their life. In most of the cases the cause remains unknown. The results presented in this dissertation might establish the basis for future studies investigating the cause of idiopathic seizures. In particular, the neuroanatomical areas described in the results might represent structures closely related with the physiopathology of seizures. Moreover, the lateralised areas described in the results might explain how hemisphere dominance affects brain microstructure and give hints of improvement for future rehabilitation therapy.

These results put the basis for future investigations of the GABRB3 gene, which was shown once more to be important for neurodevelopment and for the definition of brain features. This dissertation is, therefore, of interest for people in the world with mutations or rare variants of this gene and also for their offspring.

With respect to Angelman syndrome, a hypothetical prospect benefit will be to assess the success of gene therapy directed to the GABRB3 gene via imaging techniques targeted to the areas described in the results.

For all these reasons, these results are not only interesting for the neuroscientists, but also for the patients with epilepsy and Angelmans syndrome, and of course, for their families. Although this dissertation does not provide concrete solutions for their trouble, it certainly gives reasons to believe that future treatments and even prevention are possible.

### **C.3 Commercial activities**

Many of the pharmacological interventions for epilepsy are directed to the GABA receptors. A deeper knowledge of the structure of the GABA receptors and its influence in the brain activity and structure will definitively help in the development of drugs targeting alterations in its signalling. It is known, for example, that carriers of some polymorphisms have different pharmacodynamic and pharmacokinetic drug profiles. Here the pharmaceutical companies are expending a lot of effort and resources in this field of research. A better understanding of genetics will definitively result in better and more focused treatments. Drugs with better affinity for certain proteins and causing fewer side effects are the future prospect where the field is moving to.

The pharmaceutical industry produces millions of new compounds every year, although only a few actually reach the market. One of the reasons is that the effects in humans are completely unpredictable. In this sense, the MRI and other computational techniques can be maximised to improve drugs development. MRI, for example, has reached an important degree of technical maturity, along with enormous developmental prospects; it poses the advantages of a having a large clinical availability and being a non-invasive technique. The effects of drugs with mechanisms of action involving the brain might be tested using imaging techniques, similarly as it was done in this dissertation. Multimodal imaging, referring to the combination of techniques, fits well in the development of brain-targeted drugs due to the desirability of measuring different aspects of the brain under the same physiological conditions.

This dissertation could be used as an exemplary study for drug research. In fact, investigating a candidate gene is a similar source of controlled variance system as the use of a pharmacological manipulation.

### **C.4 Schedule and implementation**

The field of genetics has grown in complexity dramatically since its origins and promises to keep growing and showing paths for curative treatments in the future. Gene therapy is a concept that illustrates the progresses in the field; it refers to a therapeutic approach where nucleic acid polymers are provided to the cells of

a patient, similarly as a drug, to treat a disease. Individualised drugs designed according to the genome of an individual are the next step in the treatment of many other diseases. The field is moving really fast, and now is possible to sequence the entire genome of a person within hours, something that the first geneticist of the 20th century never dreamed of.

The benefits of the work presented in the thesis might probably not be seen immediately, although along with the advances in genome sequencing they will definitively be of importance in the next decade when the genetic diagnosis expands and becomes routine. A few years ago, for example, the only tool available for avoiding hereditary diseases was the preconception counselling of people affected by those diseases; now the complete genome sequencing is becoming available for the general population, allowing for an accurate preconception diagnosis even in healthy people.

After having found the importance of the GABRB3 gene in the definition of microstructure in the white matter, future genetic methods should be able to detect early mutations of this gene and correct them in order to avoid alterations of the neurodevelopment. The coming advances in the genetic techniques, along with the knowledge provided by this and other studies, can impact the diagnosis and treatment of epilepsy and Angelman syndrome in the following decade.

## C.5 Final thought

Apart from the therapeutic benefits that the understanding of genetics will bring, the knowledge is a goal itself. The question about the purpose of science has also something to do with the inherent curiosity of the human beings, and their wish to understand their world, which also applies to the interior sphere: the body. Among the many questions that have not been answered, the one about the brain occupies an important place. The Cartesian notion of a mind controlling the body has now been found to be absurd, and the notion of a unique entity mind-body emerged, with the evident consequence: the human being is, but not only, brain. As a consequence, the understanding of the human being is a process where the exploration of the brain and its functioning is crucial. The vast complexity of this organ overwhelms (but does not discourage) the researchers, and is here where it becomes evident that the creation of knowledge is a slow

process, where every bit represents a big step towards the understanding of the system as a whole.

The construction of knowledge should be the aim of all scientists, and should have as consequence the search for well-being of all human beings. This process needs to be determined by the conviction that our species will only be able to survive as a group and not as individuals. The science should not be restricted to accumulation of data and knowledge; it should also be translated into facts, with impact on our future as species and on our environment.

Since the evolution gave us the ability to alter the planet, the responsibility of transforming it in a positive way should also be one of the aims of science. The process of transformation cannot take place in isolation; respect should be paid to other species that also won the race of evolution. However, we are not in the final phases of human sciences, we are merely at a stage previous to a more advanced and refined knowledge.