

MRS of GABA: Methods and applications for understanding brain function

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Educational Course - Half Day

As we increase our use of multimodal imaging methodologies, the interest in measuring GABA to study brain function has exponentially increased. Increasing number of researchers are using MRS to study GABA and its relationship to brain function, brain connectivity, behaviour, and dysfunction. However, we are also becoming increasingly aware that measuring GABA is difficult and requires well-designed experiments, that consider the low signal to noise of GABA, sensitivity to scanner instabilities and participant movement for example. Increasing number of papers are quantifying these biases, and understanding these are necessary to design well-suited experiments that increase rigor and reproducibility of such metrics, in particular for multi-site studies. Recent developments allow for multi-metabolite, multi-region acquisitions and therefore faster editing, changing the type of experiments that can be planned in the future, as well as normalization and standardization of sequences across sites and scanner platforms as studied by one of the largest multisite studies to date (Mikkelsen et al. Neuroimage, 2016).

When applied appropriately, MRS of GABA is an incredibly useful and powerful tool to study brain function. Combining MRS with other modalities, such as task- or resting state fMRI, MEG, or behavioural metrics, has substantially changed our understanding of these functional and behavioral signals. As a neurotransmitter, much is known about the cellular and molecular systems underlying GABA function, linking macro-level functional metrics to micro-level neuroscience. MRS has also provided us with a better understanding of disorders and plasticity, providing a window into abnormal GABA mechanisms or mechanisms of plasticity in vivo. These data allow for better understanding of such disorders and possible targets for treatment or biomarkers for treatment efficacy.

After this symposium, attendees are expected to understand the methodological considerations necessary to develop and apply MRS of GABA. Attendees will gain an understanding of how GABA measurements might inform our understanding of the link between brain chemistry, brain function and behaviour, disease and finally, how MRS of GABA can provide important neurochemical information in disease.

Objective

Having completed this workshop, participants will be able to:

- Understand the current state-of-the-art for GABA MRS, and the sources of confounds and limitations of the technique.
- Identify the potential benefits of quantifying GABA to increase understanding of neural processing and behavior in health and disease
- Be able to return to their institutions and implement methods consistent with community recommended standards and critically assess MRS projects. They will have an awareness of the potential future developments of the technique.

Target Audience

This course targets all researchers who collect and analyze or aiming to collect and analyse, MRS data of GABA and other small metabolites. This is focused, but not limited to neuroscientists, clinicians and MR physicists interested in understanding the potential, limitations, and practical implementations of using MRS of GABA to increase understanding of neuronal function in health and disease.

Presentations

Introduction to MRS and Editing

Magnetic Resonance Spectroscopy (MRS) allows for the measurement of metabolic information from predefined regions of tissue. Edited MRS differs from conventional MRS in that editing pulses are applied to low-concentration molecules of interest. The focus here lies on editing of GABA, but editing can be used to examine other neurometabolites as well (including glutathione, lactate, aspartate, NAAG). During this lecture, Prof. de Graaf, author of the seminal book on MRS "In Vivo NMR Spectroscopy: Principles and Techniques" will discuss the basic principles underlying MRS in general, the shape of the MR-spectrum, and the basic principles of pulse sequences allowing for the acquisition of MRS data. He will then uncover the principles underlying editing, both from the perspective of the molecule of interest (GABA) and from the perspective of the pulse sequence. Finally, quantification and analysis of edited MRS data will be discussed. Learning aims: 1. Understand the basic principles underlying MRS 2. Understand the basic principles underlying editing of GABA 3. Understand the basic principles of quantification of (edited) MRS data

Presenter

Robin de Graaf, Yale University, New Haven, CT, United States

Limitations and Considerations for Data Acquisition, Analysis, and Quantification

Given the relatively recent emergence of MRS of GABA, guidelines for performing edited MRS are lacking and have not yet been well-established. Dr Ashley Harris will discuss pitfalls and limitations to consider when planning, analysing, and quantifying edited MRS data. This lecture will enhance the attendees' understanding of edited MRS with knowledge that can be put to practical use when designing new experiments. Dr Harris has spent the last few years establishing and quantifying such limitations. During her talk, she will discuss a variety of pitfalls and limitations including: Considerations of signal-to-noise in terms of scan time and voxel size; scanner instabilities such as dealing with motion and frequency drift; The importance of frequency and phase correction when post-processing edited MRS data, analysis and fitting of edited MRS data; limitations in multi-site applications and vendor differences; the importance of issue correction and quantification. Understanding of these factors will allow for better post-processing and greater rigor and reproducibility when planning and applying future MRS studies. Learning aims: 1. Understand how edited MRS is limited by voxel size and scan time 2. Understand how instabilities in acquisition and analysis affect data quality 3. Understand the importance of post-processing and proper tissue correction in data quantification

Presenter

Ashley Harris, University of Calgary, Alberta, Canada

MRS in the Scope of Open Science

As discussed in the previous talk, multi-site projects are problematic due to different implementations of the pulse sequences and scanner differences. Dr Oeltzschner has been involved in developing new edited sequence to substantially speed up MRS acquisition (e.g HERMES, and HERCULES) which are also available across scanner platforms and including 3T and 7T), on all scanner vendors, which will substantially enhance our ability to perform multi-site multi-vendor studies in the future. Furthermore, Dr. Oeltzschner is one of the driving forces behind MRS hub, the first online community for MRS research. MRS hub allows for community interactions, data and software sharing and generally brings together the MRS community. He has a particularly strong focus on open science and transparency in MRS acquisition, data structure, and reporting. In summary, Dr Oeltzschner will first discuss how we can increase the amount of information gained from edited experiments, and then discuss the current state of Open Science in the field of (edited) MRS. This has the potential of changing the landscape of information to be gained about brain function by using edited MRS. Learning aims: 1. Understand how new developments allow for consistency between scanners and sites to increase translatability of MRS 2. Understand the current state of Open Science in the field of MRS such that attendees understand factors that are considered important when performing transparent open MRS research.

Presenter

Georg Oeltzschner, Johns Hopkins University, Baltimore, MD, United States

The Neurochemistry of GABA and its Relation to Brain Function

While it is possible to measure GABA in the brain, the interpretation of the GABA signal remains to be discussed. Dr Caroline Rae will first introduce the neurochemistry of the GABA system, from GABA production, to release, and transport. Dr Rae is uniquely suited to do so, authoring the most widely-cited review on the neurochemistry of MRS measurable metabolites (Rae CD, Neurochem. Res. 2017). In the following part of this lecture, she will discuss how GABAergic inhibition relates to brain function and in particular, how inhibitory inputs relate to brain activity. Brain activity is a complex process, and inhibition is known to play an important regulatory role. In some cases, inhibitory input may increase brain activity (e.g the BOLD response) as interneuron activity still requires energy, whereas in other cases, it reduces the BOLD by suppressing baseline cortical activity. Dr. Rae will discuss the important interplay of excitatory and inhibitory input. Finally, she will discuss how brain GABA levels can be linked to functional metrics as measured with MEG or fMRI, as well as to behavioural metrics of cognitive function. Understanding the link between MRS GABA and the underlying function and mechanisms of GABAergic inhibition, allows for a better understanding of the origin and interpretation of the GABA signal that is measured. This understanding has changed our approach to multi-modal and translational imaging. Learning aims: 1. Understand the origin of the GABA signal 2. Understand the neurochemistry of GABA 3. Understand the basic neurophysiology of cortical inhibition and its relation to brain function and behaviour

Presenter

Caroline Rae, University of New South Wales Sydney, New South Wales, Australia

Changes in GABA, Neuroplasticity and Learning

Learning complex skills such as mastering a tennis backhand or a Chopin nocturne, critically involves plastic changes across multiple spatial and temporal scales; from the synapse to the network and from effects lasting seconds to those lasting months or even years. Only by studying modulation across these scales can we fully understand the neurophysiological basis of human learning or the re-learning of functions after a brain injury such as a stroke. MRS allows us a unique tool to study neuroplasticity and allows investigation of the synaptic changes underpinning the meso- and macro-scale changes seen with fMRI. In addition, by combining MRS of GABA with non-invasive brain stimulation (NIBS) techniques which induce neural plasticity, we can move beyond correlational studies towards causality. Dr Charlotte Stagg, a pioneer in combining MRS of GABA with plasticity-inducing protocols, will discuss what these studies have told us about human neuroplasticity, as well as their limitations. She will address the open questions in the field, and discuss what approaches may be developed to address them. Finally, NIBS techniques such as Transcranial Magnetic Stimulation (TMS) can also be used to quantify aspects of GABAergic signalling in primary motor cortex. Dr Stagg will finish by comparing the use of these techniques, describing how their combination with MRS may allow us to study specific aspects of GABAergic signalling. Learning aims: 1. Understand how changes in GABA can inform us about brain function and plasticity 2. Understand how non-invasive brain stimulation and learning approaches can inform us of the nature of the GABA MRS signal 3. Understand the limitations of studying inhibition through MRS, TMS, and behaviour

Presenter

Charlotte Stagg, University of Oxford, Oxfordshire, United Kingdom

GABA, Pharmacology, Psychiatric, and Neurological Disorders

There are large number of disorders where GABA is thought to be altered. MRS of GABA is the only technique that allows for the in vivo measurements of GABA levels in a regionally specific manner. Dr. Nicolaas Puts is an expert on measuring GABA, in particular in pediatric and other clinical cohorts. He has personally focused on measuring metabolites in children with Autism, ADHD, and Tourette syndrome. During this lecture, he will describe neurological and psychiatric disorders in which GABA is thought to be altered and discuss interpretation of these GABA differences. Subsequently, he will discuss the importance of relationships between GABA differences and clinical symptoms, clinical severity, and behavioral differences. Finally, Dr. Puts will discuss the potential of GABA-related pharmacological interventions combined with MRS as a tool to understand the neurochemistry of different disorders and predict and track treatment across time. Understanding the extent of GABA changes in the brain, and their relation to altered brain function in vivo, allows for better understanding of these disorders and possible targets for treatment. Learning aims: 1. To understand in which disorders GABA is thought to be altered and how these alterations might occur 2. Understand how MRS of GABA can play an important role in understanding neurological and psychiatric disorders 3. To understand how MRS of GABA can be used for treatment development

Presenter

Nicolaas Puts, Kings College, London, United Kingdom