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High field imaging of large-scale neurotransmitter networks: Proof of concept and initial application to epilepsy

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ABSTRACT

The brain can be considered a network, existing of multiple interconnected areas with various functions. MRI provides opportunities to map the large-scale network organization of the brain. We tap into the neurobiochemical dimension of these networks, as neuronal functioning and signal trafficking across distributed brain regions relies on the release and presence of neurotransmitters. Using high-field MR spectroscopic imaging at 7.0 T, we obtained a non-invasive snapshot of the spatial distribution of the neurotransmitters GABA and glutamate, and investigated interregional associations of these neurotransmitters. We demonstrate that interregional correlations of glutamate and GABA concentrations can be conceptualized as networks. Furthermore, patients with epilepsy display an increased number of glutamate and GABA connections and increased average strength of the GABA network. The increased glutamate and GABA connectivity in epilepsy might indicate a disrupted neurotransmitter balance. In addition to epilepsy, the 'neurotransmitter networks' concept might also provide new insights for other neurological diseases.

1. Introduction

The brain can be considered a network, existing of multiple interconnected brain areas with various functions (van Straaten, 2012). Several studies have shown that measures of connectivity between these areas can be associated with cognitive functions (Song et al., 2008; van den Heuvel et al., 2009), and that the connections are affected in several neurological diseases (Fox and Greicius, 2010; Spencer, 2002). Characterization of brain networks gained large interest in both neuroscience and neurological studies and different methods are currently being employed. First of all, methods such as functional MRI and EEG can be applied to assess the so-called 'functional networks': areas are linked together and characterized based on simultaneous brain activity. Other methods characterize brain networks based on structural connectivity, by employing diffusion MRI, thereby visualizing fiber bundles in the brain (Jones, 2008), or over individuals assessing shared distributions of cortical thickness (He et al., 2007).

One particular disease that is often studied using network theory is localization-related epilepsy (i.e. epilepsy with a presumed focal structural cause that cannot be identified historically or be seen with current imaging techniques). Although traditionally considered a focal disease, studies applying functional MRI and diffusion MRI have provided convincing evidence that localization-related epilepsy exhibits profound alterations in both local and distributed functional and structural networks (Bernhardt et al., 2013). Proper neuronal functioning and signal trafficking across distributed brain regions also rely on the release and presence of chemical components, in particular neurotransmitters. Functional and diffusion MRI cannot provide direct information on defective neurons or the associated neurotransmitter disbalance, which underlies abnormal neuronal activity, an essential feature of seizures. Insights into the neurotransmitter network dysfunction in localization-related epilepsy might be of great value to eventually better understand the neuronal network characteristics of epilepsy and also other brain diseases.

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Proton MR Spectroscopy (^{1}H-MRS) enables the non-invasive detection and quantification of metabolite concentrations in the brain, thereby offering a window on brain cell metabolism (Rae, 2014). Traditionally, neurometabolites such as *N*-acetyl-aspartate (NAA; surrogate marker of neuronal density, primarily localized in the central and peripheral nervous system) and creatine (Cr; involved in energy metabolism, often regarded as suitable in vivo concentration reference) are being measured. Aberrant levels of these neurometabolites have been found in epilepsy, but also other neurological diseases or in aging (Öz et al., 2014; Petroff, 2005). More advanced studies also focus on measurements of the inhibitory and excitatory neurotransmitters GABA and glutamate, which can be associated with neural activity (Duncan et al., 2014). However, these studies traditionally consider only local metabolite concentrations, while healthy brain functioning does not only rely on individual brain areas, but also requires proper signal trafficking, and thus relations between distant brain areas (Park and Friston, 2013). Using high-field ^{1}H-MRS imaging at 7.0 T, it is possible to obtain a snapshot of the spatial distribution of GABA and glutamate with a high (mL) spatial resolution.

Therefore, the concept of 'neurotransmitter networks' is introduced in this study. This new method relates to the assessment of coordinated spatial variations in neurotransmitter concentrations in the brain across individuals, and might be able to provide additional information on the underlying metabolic changes which affect neuronal functions. We primarily focussed on glutamate and GABA, due to their roles as important excitatory and inhibitory neurotransmitters in the brain. Additionally, NAA networks were considered, as NAA is the neurometabolite that is easiest to measure, although not directly involved in signaling. We assessed the construction and first applicability of 'neurotransmitter networks'. The concept is first applied healthy participants, and subsequently compared between patients with epilepsy and healthy participants.

2. Materials and methods

2.1. Study procedures

Two groups of participants, healthy volunteers and patients with epilepsy, were included. The exclusion criteria for both groups were all contraindications for MR scanning (such as metal implants or pregnancy), and a medical history with (other) neurological diseases. Additional exclusion criteria for the patients with epilepsy were MRI visible lesions (seen on clinical 3 T scans), changes in antiepileptic drugs (medication or dose) in the last twelve months, or a seizure frequency higher than once a month.

All participants provided written informed consent before participation. Ethical approval for this study was obtained from the medical ethical committee academic hospital Maastricht/Maastricht University, and the study was registered at the Dutch Trial Register with registration number NTR4878.

Each participant underwent a 7 Tesla MR examination (Magnetom, Siemens Healthineers, Erlangen, Germany) with a 32-channel head coil. The scanning procedure included whole brain T1-weighted imaging (MP2RAGE (Marques et al., 2010), TR/TE 4500/2.39 ms, TI_1/TI_2 900/2750 ms, FOV $173 \times 230 \times 230\,mm^3$, cubic voxel size $0.9 \times 0.9 \times 0.9\,mm^3$), a whole brain fluid attenuation inversion recovery (FLAIR) sequence (TR/TE 8000/303 ms, TI 2330 ms, FOV $166.4 \times 224 \times 256\,mm^3$, cubic voxel size $0.8 \times 0.8 \times 0.8\,mm^3$), and an MRSI acquisition. For the latter, a semi-LASER sequence was applied, which combines conventional RF pulses for slice excitation with orthogonal adiabatic refocusing pulses for volume selection (Scheenen et al., 2008). Frequency offset corrected inversion (cFOCI) pulses were included in this sequence to limit chemical shift artifacts (Ordidge et al., 1996). Other parameters were TR/TE 5520/38 ms, VAPOR water suppression, FOV $150 \times 150 \times 100\,mm^3$ (Fig. 1), and voxel size $9.4 \times 9.4 \times 12.5\,mm^3$ (1.1 mL).

Five of the healthy controls were scanned twice, with a seven-day interval, to assess the inter-scan reproducibility of the MRSI measures. Both T1-weighted and FLAIR images were checked by a neuroradiologist (P.A.M.H.) for abnormalities.

2.2. Data analysis

2.2.1. Metabolite concentrations

Before constructing the metabolite networks, the metabolite concentrations per brain area were computed. For this purpose, information from the anatomical scan and the spectra were preprocessed and analyzed (Fig. 2). With the MP2RAGE sequence, images were obtained for two inversion times: TI1 (GRE_{TI1}) and TI2 (GRE_{TI2}), which were combined to create a quantitative longitudinal relaxation time T1-weighted image (Marques et al., 2010). The GRE_{TI2} scan was skull stripped using the brain extraction tool (BET) of FMRIB Software Library (FSL, version 5.0.1) (Jenkinson et al., 2012; Smith, 2002). The T1 map was segmented in grey matter, white matter, and cerebrospinal fluid with FAST, part of FSL (Zhang et al., 2001).

To parcellate the brain into a number of standard areas, the atlas was transformed to the skull stripped T1-weighted image (Fig. 2). The atlas was defined by thirty non-overlapping brain areas (Table 1) and was created in MNI space, by combining information from the Harvard-Oxford cortical and subcortical atlases and the ICBM 2009c nonlinear symmetric template (Desikan et al., 2006; Fonov et al., 2009; Frazier et al., 2005). In addition to GM, also WM regions are included, as recent developments in the field indicate that WM has other functions than pure neuron-to-neuron communication (Butt et al., 2014). Furthermore, the presence of neurotransmitters is not only related to neuronal signaling or local synaptic activity. It has for example been shown that neurotransmitters released from axons during action potential propagation acting on glial receptors regulate the homeostatic functions of astrocytes and myelination by oligodendrocytes. Astrocytes also release neurotransmitters, maintaining signaling along potentially long axon tracts. The co-existence of multiple neurotransmitters in the WM are indicative of diverse functions important for information processing. The skull stripped T1 maps were non-linearly transformed to the MNI brain using FNIRT (FSL, version 5.0.1) (Andersson et al., 2007; Jenkinson et al., 2002; Jenkinson and Smith, 2001). The inverse nonlinear transformation was then applied to transform an atlas to each individual brain.

Metabolite spectra were analyzed using LCModel (version 6.3, Fig. 1) with a simulated basis set of 20 metabolites. The 20 model spectra (Appendix A) of acetate (Ace), ascorbate/vitamin C (Asc), aspartate (Asp), Cr, GABA, glycine (Gly), glutamate (Glu), glutamine (Gln), glutathione (GSH), glycerophosphocholine (GPC), myo-inositol (Ins), NAA, Nacetylaspartylglutamate (NAAG), phosphocholine (PCh), phosphocreatine (PCr), phosphoethanolamine (PE), taurine (Tau), scyllo-inositol (Sci), macromolecule 2.0 ppm (MM20), and the correction term for Cr (−CrCH2) were generated using VESPA (Versatile Simulation, Pulses and Analysis package, (Soher et al., 2011)). Which applies previously reported chemical shifts and coupling constants initially published by (Govindaraju et al., 2000), which were later updated (Govind et al., 2015), and refined by others including (Kreis and Bolliger, 2012; Tkac, 2008). Spectra were generated using Lorentzian lines, 1 Hz broadened, 4 kHz bandwidth, and 2048 points. Verification of the basis set included phantom experiments with varying concentrations of GABA and glutamate and visual inspection of spectra. A macromolecule spectrum acquired with a sLASER sequence (TE = 36 ms) at 7 T was initially added to the basis set, but not included in the final analysis after visual inspection. Lipids and other macromolecules were estimated using the spline function in LCModel.

Voxelwise spectra were excluded when the signal-to-noise ratio (SNR) was below 20, the Cramér-Rao lower bounds (CRLBs) of the *N*-acetylaspartate plus *N*-acetylaspartylglutamate concentrations (tNAA) was higher than 3, the CRLB of creatine plus phosphocreatine (tCr) was

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