High Resolution NMR Spectroscopy on Rat Brain In Vivo Through Indirect Zero-Quantum-Coherence Detection

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Introduction - *In vivo* NMR spectroscopy is challenging due to magnetic field inhomogeneity induced by differences in magnetic susceptibility between tissues and air. This results in broader spectral lines and hence a lower spectral resolution. Since the susceptibility-induced inhomogeneity scales linearly with the magnetic field strength it can greatly diminish the spectral resolution advantage of high-field NMR. While combinations of active, passive (1) and dynamic (2,3) shimming can substantially mitigate macroscopic magnetic field inhomogeneity, residual field inhomogeneity, as well as microscopic inhomogeneity is currently the norm. It is well-known that the evolution of zero-quantum-coherences (ZQCs) is insensitive to magnetic field inhomogeneity. Here we show that ZQCs can be used to obtain high-resolution ^{1}H NMR spectra from rat brain *in vivo* that are immune to magnetic field inhomogeneity. Furthermore, unique spectral information which is normally not directly available from regular ^{1}H NMR spectra can be extracted and used for compound identification or improved prior knowledge during spectral fitting.

Methods - All experiments were performed on a 11.74 T Magnex magnet equipped with Magnex gradients (395 mT/m in 120 μs) interfaced to a Bruker console. The final 180º pulse in the sequence 90º – t – 180º – t – 45º – t_1 – 90º – t – 180º – t2(acquisition), executed with adiabatic BIR-4 pulses, was replaced with 3D LASER localization to obtain 2D ZQC spectra from a 180 uL volume *in vitro* or on rat brain *in vivo* (TR/TE (=4t) = 1500/100 ms). Signal was acquired over 6,000 Hz with 256 t_1 increments (8 averages per increment), giving a 1,500 Hz indirect bandwidth. Unwanted coherences from uncoupled spins were eliminated through a combination of a magnetic field crusher gradient during t_1, RF pulse phase adjustment and phase cycling. In addition, water suppression was improved with three CHESS modules. 2D ZQC spectra are zero-filled to 2,048 × 2,048 and presented in absolute value mode.

Results – Extensive *in vitro* experiments (data not shown) on a sample containing aspartate (AMX spin-system) demonstrated that the aspartate spectral linewidths in the indirect F1 dimension were constant (4.1 ± 0.3 Hz) across a wide range of magnetic field inhomogeneity (water linewidth ranging from 6 to 25 Hz). Furthermore, quantitative density matrix simulations accurately predicted the observed 2D spectral patterns for aspartate (e.g. peaks resonate at frequency *differences* and are split by *passive* scalar couplings). Fig. 1 shows two regions extracted from a 2D ZQC spectrum acquired on rat brain *in vivo* (water linewidth = 19 Hz). Fig. 1A shows the *myo*-inositol (mI)/taurine (Tau) spectral region, while Fig. 1B shows the *N*-acetyl aspartate (NAA) region. With equal frequency spans in both dimensions the greatly improved spectral resolution in the indirect F1 dimension is apparent (average linewidth = 5.2 ± 0.4 Hz). Spectral fitting of the trace in the F1 dimension confirmed the known scalar coupling and frequency differences for NAA (4), but also provided novel information on scalar couplings involving the NAA amide proton.

Conclusions – A practical implementation of 2D ZQC NMR spectroscopy on rat brain has been demonstrated in which the spectral resolution in the second dimension is largely independent of the magnetic field inhomogeneity. The technique can find potential applications in the assignment and characterization of new compounds, in the detection of scalar couplings that are unresolved in conventional NMR spectra and in the acquisition of data from tissues or samples with highly inhomogeneous magnetic fields (frontal cortex, liver, breast, and most plants).

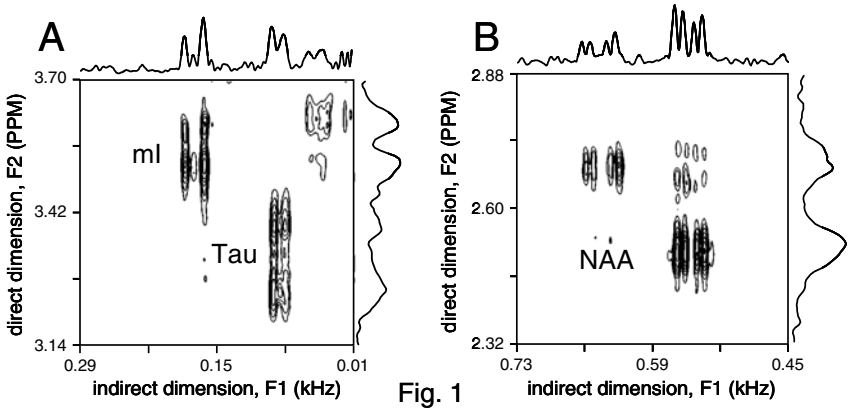

Fig. 1

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