Adapting Proton Magnetic Resonance Spectroscopy for Non-invasively Measuring Amine Neurotransmitters and their Major Metabolites in vivo

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BACKGROUND: For developmental disorders such as autism spectrum disorder and attention deficit hyperactivity disorder, there is strong evidence that the neurotransmitters dopamine (DA) and serotonin (5-HT) are key parts of disease etiology and/or pharmacological intervention. However, until now it has not been possible to systematically investigate amine transmitters or their metabolites in either normal or diseased children because available techniques for in vivo assessments, e.g., positron emission tomography, require injection of radioactive trace molecules that cannot be ethically applied to these groups. To overcome this barrier we are developing and validating an approach to signal processing in proton magnetic resonance spectroscopy (^{1}HMRS) that will allow the neurochemical basis of brain function and ultimately of brain dysfunction in developmental disorders in children to be examined in vivo in a non-invasive way. We describe here the application of a singular value decomposition (SVD) approach to ^{1}HMR spectra signal processing to measure 5-HT, its metabolite 5-hydroxyindolacetic acid (5-HIAA) and the DA metabolites HVA and DOPAC and pilot studies that combine SVD/^{1}HMRS with pharmacological stimulation to validate the specificity of these measurements.

METHOD: Nanomolar samples of 5-HT, 5-HIAA, HVA and DOPAC (Sigma Chemical Co, St. Louis, MO) were used to first identify the frequency prior knowledge/chemical shift values for these molecular moieties in vitro; these NMR frequency signatures were then used in the iterative peak alignment, estimation and mathematical filtering steps involved in the SVD-based method of signal processing. This was applied to ^{1}HMR spectra obtained in normal rats [9.4T/210 horizontal bore magnet (Magnex)] where anatomical scans (T2 MRI) were used to identify regions of interest.

RESULTS: Fourier analyses of the ^{1}HMR spectra from prefrontal cortex, caudate and hippocampus, revealed all the expected peaks (gray, Fig. 1). SVD analyses further isolated smaller peaks at the chemical shift values (ppm) for 5-HT, 5HIAA, and for DOPAC and HVA (colors, Fig 1). That these peaks reflect the intended transmitter species is consistent with the regional differences seen in their relative sizes; i.e., in the DA rich prefrontal cortex and caudate, the DOPAC and HVA peaks are larger than those for 5-HT and 5-HIAA, whereas the opposite is true for the hippocampus where 5-HT innervation is more dense than that of DA. However, further proof comes from experiments in which ^{1}HMRS/SVD was performed in rats injected i.p. with the selective 5-HT-reuptake inhibitor imipramine (75 mg/kg). In these experiments, analyses of sequential 10 minute scans reveal steady baselines for DA and 5-HT metabolites and a rapid, selective rise in 5-HIAA but not HVA or DOPAC induced by imipramine (Fig. 2).

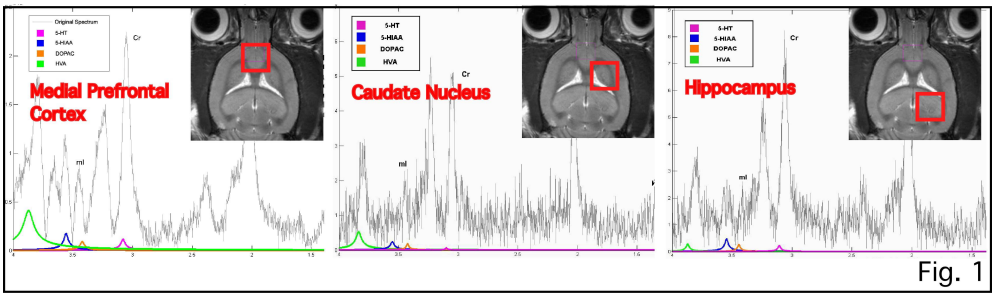

Fig. 1

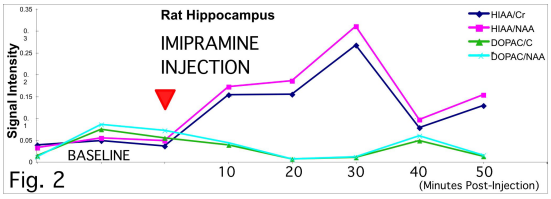

Fig. 2

CONCLUSIONS: These studies indicate that ^{1}HMRS can be brought into the new realm of measuring in vivo the amine transmitters and transmitter metabolites which as a group are notorious for known or suspected roles in nearly every form of major mental illness known, including disorders like autism that strike children. On-going studies are using additional pharmacological agents to confirm the identities of other SVD transmitter peaks and piloting the approach to humans to open up the as yet unstudied area of in vivo assessment of neurochemistry in the living, developing human brain in health and disease.