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Brain choline in major depression: A review of the literature

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ABSTRACT

The focus of this review is to provide a synthesis of the current literature on the role of brain choline, as measured by proton magnetic resonance spectroscopy (1H-MRS), in major depressive disorder (MDD). The most recent ^{1}H-MRS literature review took place over 10 years ago and, reflecting the high level of research on this topic, much has been learned since then. Higher brain choline levels have been linked to an increase in depression, and a cholinergic model for MDD development has been postulated. However, current ^{1}H-MRS studies have been inconclusive regarding the role of choline in depression. Data from eighty-six peer-reviewed studies were analyzed for a random-effects model meta-analysis. Two significant findings are reported. Papers that did not report segmentation had a significant, moderate effect size. Higher choline concentrations in the frontal lobe were found in depressed patients, both in those who responded to treatment and those who did not, after treatment with psychiatric medication, repetitive transcranial magnetic stimulation, or electroconvulsive therapy. Findings from this review may add to existing information regarding the role of brain choline in MDD. This may provide a future target for treatment and drug development. It also may serve as a biomarker for treatment progress.

1. Introduction

Choline is an endogenous compound considered by the Institute of Medicine to be an essential nutrient (Finglas, 2000). It has a number of important functions in the human brain, including serving as a precursor for phospholipid synthesis and facilitating cholesterol transport (Zeisel and Da Costa, 2009). Choline is also integral to the production and release of acetylcholine (Zeisel, 2006), a critical neurotransmitter that mediates memory storage. Ten years ago it was reported that reduced perinatal choline intake may have enduring effects on cognitive function in terms of memory capacity and functional attention in neonates (Meck and Williams, 2003). Choline has a profound impact on the developing brain, and any choline irregularities in development have the potential to prove disruptive. In adults, increased choline levels have been associated with several neurodegenerative conditions including multiple sclerosis and adrenoleukodystrophy (Murata et al., 2001).

Proton Magnetic Resonance Spectroscopy, or ^{1}H-MRS, is a non-invasive in vivo brain imaging technique that has been used to measure concentrations of several neurometabolites in the brain - specifically, N-Acetyl Aspartate (NAA), Creatine + phosphocreatine (Cr), Glutamate (Glu), *gamma*-Aminobutryic acid (GABA) and Choline-containing compounds (Cho).

In brain, the MRS visible Cho resonance primarily arises from phosphocholine, detected at 3.21 ppm (ppm) and glycerophosphocholine (3.23 ppm), with much smaller contributions from free choline (3.21 ppm) and acetylcholine (3.21 ppm) (Miller et al., 1996; Sabatier et al., 1999; Verma et al., 2016) (see Fig. 1). Importantly, phosphatidylcholine does not contribute to the ^{1}H-MRS choline resonance (Chmelik et al., 2015). It has been suggested that higher choline levels may reflect increased cell membrane turnover (Ende et al., 2000).

In ^{1}H-MRS, the resonance arising from choline-containing compound levels is commonly reported using one of two methods. Historically, it was thought that the 3.0 ppm brain Cr resonance levels would be relatively stable across brain regions and individuals, and therefore the metabolite ratios to brain total creatine would correct for the variable excitation across brain regions during MRS. However, accumulating evidence suggests that creatine concentrations might not be as consistent as originally thought and so, despite the technical challenges, obtaining absolute choline concentrations may be more accurate, albeit more time consuming (Jansen et al., 2006).

In terms of mood, there is a cholinergic-adrenergic hypothesis of depression, postulating that greater acetylcholine levels and increased cholinergic signaling may result in depression (Janowsky et al., 1972). Though the acetylcholine signal contributes relatively little to the ^{1}H-MRS choline signal, recent research suggests a strong correlation may

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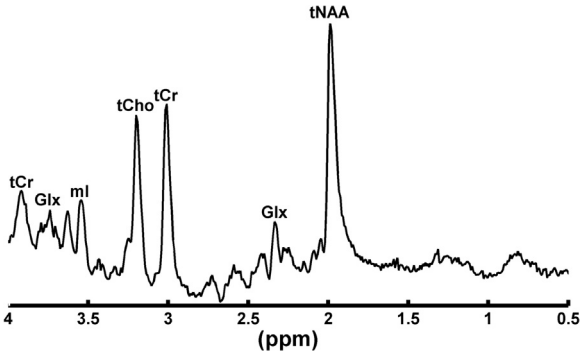

Fig. 1. MRS spectrum showing the peak from which total Choline is derived. Contribution to Choline signal, in terms of micromoles/kg: Free choline: 25, phosphocholine: 380, glycerophosphocholine 400, phosphatidylcholine 14,700 (Miller et al., 1996).

exist between the ^{1}H-MRS signal of choline and acetylcholine, derived via microdialysis and high-performance liquid chromatography in the hippocampus, striatum, frontal cortex of rats (Wang et al., 2008).

^{1}H-MRS studies have noted alterations, both increases and decreases, in the intensity of the choline resonance of individuals with major depressive disorder (MDD). Some investigators have reported that mood may be influenced by cholinergic as well as adrenergic control (Cohen et al., 1982). Moreover, choline-containing substances have been shown to reduce manic symptoms in bipolar disorder (Cohen et al., 1982; Stoll et al., 1996).

However, recent work has noted both increases and decreases in brain ^{1}H-MRS choline in depressed populations. These studies vary in terms of sample, study design, brain structure or region examined, and the type of brain matter studied (e.g. gray vs. white matter). A 2006 meta-analysis, as a part of a larger ^{1}H-MRS review, reported that MDD patients had higher ratios of choline to creatine (Cho/Cr) in the basal ganglia than healthy controls (Yildiz-Yesiloglu and Ankerst, 2006). This finding was challenged in a subsequent review, finding mixed results in the basal ganglia, with elevated Cho values being reported only in the putamen (Rao et al., 2011). More recent reviews have noted no significant differences in frontal lobe Cho in adults and have found varying results in pediatric mood disorder populations (Arnone et al., 2015; Coupland et al., 2005; Hulvershorn et al., 2011). However, no review, to our knowledge, has focused on choline in ^{1}H-MRS depression studies, and, furthermore, the most recent meta-analysis of ^{1}H-MRS studies in depression was published in 2006, since which time much has been learned about choline, depression, and MRS techniques (Yildiz-Yesiloglu and Ankerst, 2006). This is also the first literature review/meta-analysis to include both pediatric and adult populations, which is significant because many cases of MDD develop in or before adolescence (Costello et al., 2006). Also, in light of the disparate reports of Cho in the MDD literature we felt it useful to re-examine the literature in order to elucidate the role that Cho plays in the brains of both adult and pediatric patients with MDD, and what, if any, differences exist between the two populations.

2. Methods

2.1. Search strategy and inclusion/exclusion criteria

A literature review was conducted on PubMed using the search terms *pediatric AND MDD AND choline; MRS AND choline AND pediatric: depression AND MRS AND choline; MDD AND choline; Choline AND MRI; proton spectroscopy AND MDD AND choline.* We also obtained papers by cross referencing literature reviews on ^{1}H-MRS for papers on choline that we may have neglected, as well as other papers. These search terms along with the referencing of literature reviews seemed to yield all available papers on ^{1}H-MRS studied choline in MDD to date. To be included in analysis, papers had to report on ^{1}H-MRS acquired Cho or Cho/Cr values from MDD patients. Since we were interested in the role of choline in MDD, we limited our papers to those who reported some sort of choline value, as studied by ^{1}H-MRS. Papers were excluded from our meta-analysis if there was no available English translation of the papers. Furthermore, though literature reviews were reviewed, values from the literature reviews were not included in statistical analyses, as this would have complicated our data. Along with Cho or Cho/Cr mean values, average participant age, voxel of interest location, number of subjects, field strength, Cr, voxel size, voxel segmentation and Time of Echo (TE) were collected in a database for further analysis.

2.2. Meta-analysis

In meta-analyses, standardized effect sizes are often calculated to compare differences in means among studies. The three most commonly used effect size metrics in meta-analysis are Pearson's correlation coefficient, *r*, Cohen's *d* and the odds ratio (Field and Gillett, 2010). For our purposes, Cohen's *d* was chosen for the effect size metric because it is based on the standardized difference between two means, reflecting the differences in mean neurometabolite levels between controls and depressed individuals (Cohen, 1992, 1988; Field and Gillett, 2010). Cohen's *d* was also chosen as the effect size metric for this study because it is better at accounting for large group size variance, something characteristic of published ^{1}H-MRS studies (McGrath and Meyer, 2006).

The means and sample sizes of depressed and control groups were used to compute Cohen's *d* for Cho, Cho/Cr, and Cr in both pediatric and adult studies.

Equation for Cohen's *d*:

$$d = \frac{M_1 - M_2}{SD_{pooled}}$$

An effect size or sizes were calculated from each paper; papers that had similar regions of interests, were averaged together, so as to avoid one paper skewing results as suggested by Rosenthal (Rosenthal, 1991). For example, if a paper reports Cho concentrations in the left and right dorsolateral prefrontal cortex (DLPFC), then an effect size was calculated between the depressed group and control for each side, and then these two effect sizes were averaged together – giving a calculation for the DLPFC. The same was true when there were multiple groups, such as mildly or moderately depressed. However, effect sizes were not averaged together between brain volumes comprised of differing tissue content or from differing brain lobes. Preliminary analysis showed that the segmentation of the voxel may significantly affect neurometabolite concentration, and so, to avoid this particular confound, gray matter and white matter effect sizes were not averaged together. Further analysis showed that indeed cholinergic values differed from white matter and gray matter, especially in Cho/Cr values. This suggests the importance of voxel segmentation analysis when collecting ^{1}H-MRS data.

2.2.1. Method of meta-analysis

Meta-analysis can be done using a fixed-effects or random-effects model and there is debate about which is the most appropriate (Field and Gillett, 2010; Hedges and Vevea, 1998; Hedges, 1992; Hunter and Schmidt, 2000). Field suggests that greater error occurs from applying a fixed-effects model to a random-effects data than from applying a random-effects model to fixed-effects data (Field and Gillett, 2010). Furthermore, a random-effects method is most appropriate when wishing to generalize findings beyond the studies included and when there is large variance in effect sizes (Field and Gillett, 2010). We therefore felt it most appropriate to use a random-effects model for our meta-analysis. Hedges and Vevea's (1998) random-effects model was applied to Cohen's *d* effect sizes through publicly available SPSS syntax written by Field (2010). Rosenthal's Fail-Safe N was calculated to address the "file-drawer problem" (Rosenthal, 1979). Also, Begg and Mazumdar's rank correlation test was calculated for each random-