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• REVIEW •
Special Focus on Brain Imaging and Addiction

Proton magnetic resonance spectroscopy in substance use disorder: recent advances and future clinical applications

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Abstract Proton magnetic resonance spectroscopy (1H-MRS) now is widely used in clinical researches for the measurement of compounds or metabolites in vivo, especially in neuropsychiatric diseases/disorders. Recently, there are many studies on substance use disorders utilizing 1H-MRS to explore the mechanism of brain metabolites. It is found that metabolites levels in substance users are changed compared with healthy controls. Furthermore, these changes also relate to behavior indices, and provide evidence for the impact on neuronal health, energy metabolism and membrane turnover. However, 1H-MRS is not yet a mature detection technology, and it still has many challenges in the application of the neuropsychiatric disorder area. The settings of test parameters and the inconsistency of results across different studies still plague the clinicians and technicians. This article is intended to provide an overview of basic theory and methods of 1H-MRS, and the literature reporting metabolites alterations in substance dependence, as well as the related neuropsychological performance. At last, we will discuss the forthcoming challenges and possible future direction in this area.

Keywords proton magnetic resonance spectroscopy, substance use disorders, brain imaging, neurometabolites

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1 Introduction

As a non-invasive method, proton magnetic resonance spectroscopy (1H-MRS) detects the brain features by using the abundance and magnetic resonance sensitivity of proton in the strong field [1]. Different from MRI, which aims to obtain anatomic images, 1H-MRS uses magnetic resonance signals to obtain biochemical information in the specific living tissues. It could also provide information of metabolite concentration in predefined brain areas. The metabolites that could be measured include choline containing compounds (Cho), creatine (Cr), inositol and glucose (both sugars) and N-acetylaspartate (NAA), as well as neurotransmitters in glutamatergic system. These metabolites in the spectrum have diversified peaks (specific frequencies). 1H-MRS could be used to determine the consequences of brain diseases and subsequently observe the patient's prognosis. MRS has been currently used in many medical researches,

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such as neurological diseases and mental disorders [2]. As a chronic brain disease, substance use disorders (SUDs) is characterized by drug-taking behaviors with compulsivity and impulsivity, as well as higher risks of relapse [3, 4]. Now it is a serious problem of public health around the world, which causes the huge healthy burden [5], and it is reported that there are about 2.75 billion people who suffered from drug abusing history during their lifetimes [6]. There are many substance use-related neurotransmitter hypotheses and findings, involving different stages of substance dependence [7]. Recently, MRS plays an increasingly important role in the exploration of the neurotransmitter mechanism of SUDs [8]. Up to now several 1H-MRS studies have examined the regional metabolites concentrations in patients with SUDs, comparing with healthy controls and light users. However, there is still a certain time interval and technical distance between practical application of MRS and clinical studies. This review will present a brief overview of the several technical issues related to 1H-MRS measures, the key findings of SUDs from the aspect of 1H-MRS, and the relationship between neurometabolites alterations, clinical features and cognitive performances. Then, we will discuss the challenges of MRS application in substance dependence area.

2 Parameter details of 1H-MRS

MRS is a non-invasive method for in vivo molecules investigation, which utilized the means of resonance frequency and spectral patterns. In living tissue, hydrogen nucleus (proton, 1H) has the largest abundance and it also has the highest MR sensitivity, so in vivo MR applications the proton holds an exceptional position [9]. Therefore, it is also the most common in the literature reports. The protons play the role as tiny magnets in tissue and then they are aligned in the parallel or antiparallel magnetic field of an MR scanner. Transmitter and receiver coils of the MR scanner are used to apply radio frequency pulses with the hydrogen resonance frequency to induce the hydrogen nuclei to a higher energetic state [10,11]. Then the hydrogen would return to its magnetic equilibrium state and emits the previously absorbed energy, when turned off these pulses. These state switched in turn and it could be detected by receiver coils [1]. Diversified techniques will be applied to acquire the spectrum, ranging from single-voxel spectroscopy (SVS) to spectroscopic imaging (MRSI), which acquire imaging with multi-voxel. Usually, anatomic images are also acquired before 1H-MRS, and the structural MRI is used to set a volume of interest (VOI). The SVS technique is the most basic and most widely used method, in which the signal is obtained from a well-defined volume, and there are two typical acquisition modes: pointed resolved spectroscopy (PRESS) and stimulated echo acquisition mode (STEAM) [12, 13]. As a multivoxel technique, MRSI can acquire spatial and spectral information in the same measurement process and combines biochemical information with anatomical structure. Besides, 1H-MRS can be obtained using different TEs, with distinct spectra in result, which should be based on the metabolite of interest [1]. In clinical studies, most short-TE designs select about 30 ms (from 20–40 ms), while long TEs range from 135 to 288 ms (135 ms is the most used). Short-TE could bring a high SNR and less signal loss, while long-TE has more simple spectra because it suppresses some signals (however, the SNR also decreases).

3 Measurable metabolites in 1H-MRS

The most commonly observed resonance peaks in 1H-MRS are NAA, Cr, Cho, myo-inositol (MI), gamma-aminobutyric acid (GABA), and Glx, and each metabolite provides specific information about the function of neurons, cellular structures, as well as some molecules that are involved with neurotransmission. NAA peak is observed at 2.02 ppm in the spectrum, which is considered a putative marker of the number of neurons, and reduced NAA has been for a long time interpreted as reflecting neuronal death. NAA is observed to be reduced in some brain diseases/disorders, such as intracranial tumors [14], epilepsy [15], schizophrenia [16], and depression [17], as well as SUDs [18, 19]. The Cr resonance peak at 3.02 ppm contains both Cr and phosphocreatine (3.94 ppm). Cr is converted to a high energy phosphate (phosphocreatine) and is critical in brain energy metabolism. Cr was also widely focused in many studies in

SUDs [20, 21], which has been proved to be related to brain metabolism. Cho play an important role in the synthesis and degradation of cellular membranes, which is observed at the peak of 3.2 ppm, and is considered sensitive to changes in membrane phospholipid metabolism. Its role in SUDs is still under discussion [20, 22]. At the resonance peak of 3.56 ppm is MI, which is considered as a glial marker. Glx (glutamate and glutamine) located the peak at 2.40 ppm (2.05–2.50 ppm) [23]. Glx plays an important role in brain metabolism as a primary excitatory neurotransmitter, while GABA as the inhibitory one was detected at 3.03 ppm. Changes of this glutamatergic system were also discovered in many 1H-MRS studies about SUDs [24,25]. However, the detection and quantification of these metabolites below 7 Tesla (T) field usually require some post processing methods, because of low concentration, complicated multiplet structures, or partial superposition of resonance peaks [11].

4 Metabolites concentrations in different SUDs patients

The results reported by different studies vary widely. Table 1 [18, 19, 21–102] summarized the results of currently published articles. According to the results reported by most articles, present review discusses the changes of neurometabolites in different substance dependence.

4.1 Alcohol

There were many 1H-MRS studies of alcohol dependence. As previous researches reported, NAA and Cho were noted as lower ones in frontal gray matter and frontal white matter of alcohol-dependent subjects, comparing with light drinkers after one week of abstinence [103]. Another study also noted an increase in front mesial NAA values at six to seven weeks of abstinence [54]. Relative to the baseline, an increase in Cho levels with one to three months of abstinence was observed in the cerebellum and the frontal lobe [54, 56]. There was a trend of reduced NAA levels in patients with severe alcohol withdrawal symptoms more than two weeks [18]. Furthermore, comparing with light drinking subjects, elevated Cr with recovery was only reported in alcohol-dependent subjects in parietal gray matter [104]. Not only in human but also in animal models of alcohol addiction, NAA, Cho and Cr have been repeatedly assessed by MRS and were found to deviate from levels in healthy animals [24]. It seems that there might be a potential to recover in brain during abstinence. However, some evidences appeared to be inconsistent. No difference was observed in the values of NAA and Cho in the occipital cortex [105], left cerebellar hemisphere, or medial prefrontal cortex, when compared with healthy subjects [54]. Similarly, during the six months follow-up, there is no significant increase of NAA that could be detected [56]. Moreover, Bartsch also indicated that MI had no changes in infra- or supre-tentorial with four to five weeks of abstinence from alcohol, compared with those at one week of abstinence. The levels of NAA, Cho and creatine in ACC were also found not significantly different between healthy controls and patients in inpatient detoxification centers [55]. As for glutamate and glutamine, most studies showed that they were changed. The study in 2011 reported that ACC glutamate was decreased in alcohol-dependent males after 2 weeks of abstinence [24]. There was a positive correlation between ACC glutamate levels and patients' breath alcohol levels [24]. Bauer and colleagues also found that craving of patients was associated with Glx levels in the ACC [55]. This suggests that the level of glutamatergic metabolites may reflect the body's alcohol level and the patient's immediate craving for alcohol. On the other hand, GABA concentrations did not differ in most studies [85, 106, 107]. The result is unexpected. It is generally believed that the glutamate-GABA balance is involved in the formation of alcohol dependence [108–110]. However, it may suggest that this disordered balance is dominated by abnormal glutamate levels. Perhaps, these findings may overall provide evidences of neuronal recovery in abstinence, though there are inconsistencies in 1H-MRS alcohol studies. The possible explanations for the inconsistencies in study findings may contain the different abstinent periods to the time point of MRS scans, as well as the variations of control group settings (health control, light drinker or self-baseline). It is also possible that demography and clinic features, such as social-economic status, onset-age of alcohol dependence or severity of dependence, also

Table 1 Summary of reported neurometabolites changes in substance dependence[a)]

		Glx	Glutamate	GABA	NAA	Cho	MI	Cr
Alcohol [18, 24, 26–57]	Decrease	ACC	ACC, PVC, MPFC	ACC, OCC	FWM, TH, ACC, PVC, CB, PFC	ACC, FWM, CB	–	ACC, FWM, CB
	Increase	–	OFC, ACC, PFC	–	–	OFC, PVC, FWM, OCC	PVC	–
	NA	HP, ACC, POC, DLPFC, CB	ACC, FWM, TH, DLPFC, POC, ACC, Insula	ACC, DLPFC, POC, ACC	ACC, HP, DLPFC, OFC, POC, ACC, PC, MPFC, Insula, FWM	ACC, FWM, TH, DLPFC, POC, ACC, MPFC, Insula, CB	ACC, DLPFC, POC, OWM, TL, ACC, MPFC, Insula, FWM, CB	ACC, FWM, TL, DLPFC, OFC, POC, ACC, MPFC, Insula, FWM, CB
Nicotine [58–61]	Decrease	–	–	–	–	ACC	–	–
	Increase	ACC	–	–	–	–	–	–
	NA	–	ACC, HP	ACC	ACC	–	ACC	–
Amphetamine-type [19, 22, 62–81]	Decrease	ACC, Precuneus, IFC, BS	MPFC	–	DLPFC, ACC, MPFC, BG	ACC	–	PFC, BG
	Increase	FWM	BS	–	–	FWM, ACC	FWM, PC	FWM
	NA	BS, DLPFC, FWM, ACC, PFC, TH, BG, OCC, MPFC, PC	DLPFC, FWM, ACC, MPFC	–	BS, FWM, ACC, BG, PVC, TH, MPFC, HP, OCC, PC, DLPFC, ACC	BS, BG, PVC, DLPFC, ACC, FWM, MPFC, TH, OCC, PC	DLPFC, FWM, ACC, MPFC, BG, TH, OCC	BS, MPFC, ACC, BG, TH, FWM, PVC, OCC, PC
Opioids [82–88]	Decrease	ACC	DLPFC	–	DLPFC, ACC	–	DLPFC, ACC	DLPFC, ACC
	Increase	–	NAc, ACC, OFC, POC	–	–	–	–	–
	NA	ACC	–	DLPFC, ACC, POC	OFC, POC, ACC	DLPFC, ACC, OFC, POC	POC, ACC	OFC, POC, ACC
Cannabis [65, 89–96]	Decrease	–	ACC	ACC	ACC, DLPFC	–	ACC	ACC
	Increase	–	–	–	VLPFC	–	–	–
	NA	HP, BG	HP, BG	–	BG, TH, HP, ACC, BG	BG, ACC, DLPFC, TH, HP, BG	BG	
Cocaine [21, 23, 25, 97–102]	Decrease	–	ACC	PFC	MPFC, TH, FWM	TH	–	–
	Increase	–	ACC	–	BG	ACC, DLPFC	MPFC, FWM	–
	NA	BG, ACC	MPFC, ACC, DLPFC	ACC, DLPFC, BG	ACC, DLPFC, PFC, BG	MPFC, ACC, PFC, BG	ACC, DLPFC	MPFC, ACC, DLPFC, BG

a) ACC: anterior cingulate cortex; BG: basal ganglia; CB: cerebellum; DLPFC: dorsolateral prefrontal cortex; FWM: frontal white matter; HP: hippocampus; MPFC: media prefrontal cortex; NAc: nucleus accumbens; OCC: occipital cortex; OFC: orbital prefrontal cortex; PFC: prefrontal cortex; POC: parietal and occipital cortex; PVC: primary visual cortex; TH: thalamus; TL: temporal lobe; Cho: choline; Cr: creatine; Glx: Glutamate+Glutamine; MI: myo-inositol; NAA: N-acetylaspartate; PC: parietal cortex.

contribute to inconsistencies. As reported by Prisciandaro and colleagues, AUD participants' glutamate and NAA concentrations were inversely associated with their number of heavy drinking days [106].

Furthermore, the duration of alcohol use, rather than daily consumption, predicted greater concentrations of Cho, Cr, Glx, and NAA [20]. However, these results were not consistently reported across all studies.

4.2 Nicotine

The neurometabolites of interest in 1H-MRS research on nicotine use mainly includes glutamate and Glx, and there are also some studies focus on NAA and Cho. Generally, the findings of these studies indicated that nicotine use resulted in changes of neurometabolites in brain. For instance, Mennecke et al. [61] found that Cho/Cr significantly decreased in left cingulate cortex in smokers compared with non-smokers, but there was no differences in the NAA level. In contrast, Gallinat et al. [111] in 2007 reported that NAA levels reduced in left hippocampus of nicotine users, and higher Cho concentrations ACC with increased lifetime nicotine exposure. The study in female nicotine users showed that subjects who relapsed had a reduced glutamate/Cr levels in dorsal anterior cingulate cortex when compared with non-relapse users [112]. But another study published in 2007 presented with the inconsistent results. There were no differences in anterior cingulate cortex and hippocampal glutamate levels between nicotine-dependent subjects and healthy controls [60]. In regard to such different results, the factor of gender in glutamate concentrations might be considered. It could also be possible that treatments had some impact on relapse and glutamate level. The study in 2011 [112] scanned with magnetic field of 4 T and in 2007 was 3 T [60]. From the aspect of 1H-MRS methods, the measurement of glutamate requires relatively high field [11], and the difference of magnetic field strength may bring inconsistent results.

4.3 Amphetamine-type stimulants

1H-MRS is also widely used in amphetamine-type stimulants (ATS) studies of different brain regions, and there are many evidences for the change of metabolites concentrations in ATS usage. Many studies reported that alternations of NAA was observed in methamphetamine (MA) dependence patients, though contrast group settings were different. Comparing with healthy controls and patients after long-term abstinence, NAA values reduced in anterior cingulate cortex of patients with short-term abstinence [19,22, 78,113]. These results may imply neuronal injury and cholinergic changes with chronic MA use. Moreover, some studies also showed that in ACC, the ratio of Cho/NAA increased in recent abstinence, related to longer periods of abstinence [76, 78, 80], while a decreased Cho value observed in the right dorsolateral prefrontal cortex in both active users and abstinent users of three months [22]. Furthermore, changes of MI with MA use were reported, that MA users had higher MI levels in frontal white matter and right ACC while controls did not [19]. This finding might demonstrate the increased cell proliferation in MA-related neurotoxicity [67]. The MI increase was also noted in 3, 4-Methylenedioxymethamphetamine (MDMA). In basal ganglia MDMA users had higher MI levels than control, which might provide the evidence that in MDMA use glial had some responses [114]. As for glutamatergic system, short-term MA-dependent subjects showed lower glutamate and Glx levels in medial prefrontal cortex [63], frontal gray matter [76], precuneus and right inferior frontal cortex [62]. On the contrary, there is an increase of Glx values with longer periods of abstinence from MA [76]. Though there are many evidences for metabolites changes in MA usage, the inconsistencies were showed in the MA and 1H-MRS study findings, especially the results of NAA and Cr. In both recovering and active MA-dependent patients, no NAA difference was observed when compared with healthy subjects in ACC, as well as frontal white matter, basal ganglia and primary visual cortex [76,83]. Also, Cr was noted to have no differences in concentrations between MA-dependent and healthy subjects [78, 83, 113]. Most of the studies indicated that metabolites levels changed in MA-dependent patients. We may consider that the inconsistent results come from varieties of brain regions and different field strength. However, when some studies measured similar brain regions with the same field strength, inconsistent findings were also reported, which suggests that more clinical features should be concerned. These features range from age, duration of MA use, daily dose and frequency of MA use,

to polysubstance use. For example, it was found that glutamate levels in brainstem are significantly elevated in patients with MA use disorders, and are significantly associated with duration and dose of drug use [81].

4.4 Cocaine

Most of the 1H-MRS studies in cocaine use indicate the neurometabolic alterations. There are differences in brain metabolites among cocaine-dependent patients and healthy controls, containing NAA, MI, Cr and glutamatergic metabolites. The early study in 1997 showed that the elevated Cr and MI in the white matter were associated with cocaine use, while NAA was not different from health controls [115]. Interestingly, in 2017 a study reported in the prefrontal cortex cocaine users exhibited a decrease in NAA relative to healthy control subjects [21]. Also, cocaine users exhibited higher glucose/total Cr ratios than controls in the pregenual ACC and higher Cho/ Cr ratios in the pregenual ACC and right DLPFC [100]. In glutamatergic system, lower levels of glutamate concentrations in ACC and prefrontal cortex [21], and lower GABA in frontal lobe were observed in cocaine users when compared with healthy controls [25, 101]. However, a study in 2012 reported that Glu levels in the dACC were significantly higher in cocaine-dependent patients compared with healthy controls [102]. On the whole, the results from these studies demonstrate that cocaine use was associated with altered metabolites concentrations, such as cortical glucose metabolism, membrane turnover and glutamate cycling. From early 1H-MRS study in cocaine to the recent one, there are more than 20 years of history and the technology of MRS is largely developed. The development of MRS scanning might explain part of the differences across the reported results. On the other hand, there are heterogeneity of participants in these studies. Features such as duration of abstinence, polydrug use, and other factors in demography should be considered when reviewing these findings. However, this information was hard to evaluate and compare in practice. Establishing a shared online database like the Enigma database and integrating original data for analysis may be an effective way [116].

4.5 Opioids

In opioid use disorders most studies focused on Glx, while other metabolites were less reported. There were also some 1H-MRS studies combined functional MRI, or measured neurometabolic alterations during intervention. Compared with control group, opiate-dependent individuals had lower concentrations of NAA, Glu, Cr, and MI in the DLPFC. Lower NAA, Cr, and MI were also reported in the ACC [85], while the level of GABA concentration did not differ between groups in any region. In another study, glutamate concentrations in the NAc were significantly higher in prescription opiate users than in controls [82]. Moreover, in frontal white matter, Cho concentrations were found increased in opiate-dependent patients related to healthy controls. Glutamate in the ACC was also positively associated with the number of previous withdrawals [84]. For Glx, a significant group-age interaction was found. Whereas Glx declines with age in healthy controls, Glx increases with age in opiate-dependent patients. Besides, in a combined spectroscopic and functional MRI study, reduced concentrations of dACC N-acetylaspartate and glutamate/glutamine were observed [88]. These findings suggest that the dACC is biochemically and physiologically abnormal in long-term opiate-dependent individuals. Interestingly, methadone prescription (i.e., classic medication for opioid dependence) was found to be associated with increased NAA and glutamate/glutamine levels in dACC, and decreased MI levels in dACC [87]. In addition, methadone maintenance dose also modulate ACC glutamate levels in heroin-dependent individuals [83]. It indicated that methadone not only acts on opioid receptors but also is involved in mediating other neurotransmitters.

4.6 Marijuana

There were not many 1H-MRS studies on marijuana-use, and the evidence for the effects of marijuana use on brain metabolites was limited. The adolescent marijuana-using cohort study published in 2013 showed significantly lower ACC GABA levels, which paralleled significantly lower ACC glutamate levels [96].

These effects, which were worth noting, remained significant after controlling for age and sex. The present spectroscopic findings support functional neuroimaging data documenting cingulate dysfunction in marijuana-dependent adolescents. Glutamatergic and GABAergic abnormalities potentially underlie cingulate dysfunction in adolescent chronic marijuana users. However, another study published that year found no overall group effects between young-adult marijuana users and healthy controls, though two metabolites showed effects of group by sex interactions [95]. It is found that lower levels of Glx/Cr were observed in female, but not male marijuana users compared with controls, and higher levels in MI were observed in female users compared with female non-users and males in both groups. Also, there are the two studies that reported no group differences in most neurometabolites among marijuana users and healthy control subjects [92]. However, for the distribution of MI/Cr, it exhibited higher MI/Cr in WM than GM, which was not observed in marijuana users. Moreover, lower MI [93] and ratio of MI/Cr [92] in chronic marijuana users were observed when compared with healthy volunteers. These limited findings indicate that there might be decreased glial proliferation as a result of marijuana use, but further researches are needed.

5 Relationship between brain metabolites and behaviors

5.1 Substance use, craving and relapse

There is a great number of studies that reported changes of neurometabolites in SUDs. However, what should be paid more attention to is the relationship between metabolites and behaviors of the patients, which are more relative to diagnosis and treatment. As the core feature of substance dependence, craving and relapse are associated with deviation of neurometabolites. In alcohol-dependent patients, elevated glutamate in DLPFC was associated with higher cravings for alcohol and lower NAA concentration of parietal area was predictive of relapse outcome [117,118]. Accumulated time of cannabis use in cannabis users were also significantly associated with NAA concentration in Broca's area [119]. Nicotine smoker exhibited significantly reduced dACC MRS glutamate when compared with abstinent individuals [112]. ACC glutamate levels were also inversely correlated with heroin use in heroin-dependent users [83]. For MA users, MA use is associated with a significant increased Glu level and reduced NAA level in the mPFC [120]. Recent studies have found several interesting but scattered results, the implication value remains limited, mainly due to the lack of standardized large-scale cohort studies and sufficient reliable evidences.

5.2 Cognitive function

Changes of neurometabolites are also correlated with cognitive function of patients with substance dependence. In alcohol use disorders, some studies explored the association between neurometabolites and attention processing in alcohol users with neuropsychological testing. The research reported the increase of medial prefrontal NAA accompanied by improvements in attention [54]. Moreover, in nicotine users it was found that Cho level was related to lifetime nicotine use, which might indicate that nicotine use could cause acceleration of the membrane turnover cortex and the changes in cell density [111]. As for ATS-use, the association between metabolites changes and cognitive performance has been observed. Some studies reported that poorer cognitive performance, like attention and spatial ability, was associated with lower NAA level in ACC and the primary visual cortex [78, 80]. In opiate users, deficits in DLPFC NAA and Cho and abnormality of ACC Glu were correlated with poorer working memory, executive, and visuospatial functioning. Elevated OFC Glu and Cho, and lower Cr was suggested to relate with higher non-planning impulsivity [85]. Furthermore, impulsivity was also found to be positively related to Glu levels in cocaine users [100]. It is also observed that abstinent cocaine users were significantly worse than healthy controls on the trail making test and performance on this task was inversely related to NAA levels [21]. All these evidences from behavior test suggest that there are substantial changes in brain

metabolites that impact on cognitive functions, though these changes of metabolites are inconsistent in patients using different type of substance, as well as different brain regions.

6 Challenges and future direction

In decades of MRS application in the field of substance dependence, it is of great significance for elucidating the pathological features of the disease. At the same time, previous studies suggest that it is also valuable to apply MRS to the diagnosis and clinical outcome prediction of substance dependence. However, until now, the application of MRS in substance dependence has not yet reached maturity in clinical application, mainly because several challenges still remain to be solved. With the development of physical technology, there are also many possibilities to explore and promote MRS.

6.1 Increase the measurement reliability of MRS method

Although large scale MRS data of substance use disorder have been collected, few studies concerned the measurement reliability of their MRS evaluation, with large or small sample. Measurement reliability is the typical blind but important area in neuroimage studies [121, 122]. In MRS studies of the population other than substance-dependent patients, several factors may influence the reproducibility of the results. MRS sequence is the most important one. For instance, Baeshen and colleagues suggested that only MEGA-PRESS sequence has moderate test-retest correlation in GABA evaluation, while JPRESS and PRESS were less than satisfactory [123]. PRESS and MEGA-PRESS sequence have higher test-retest reliability in Glx evaluation than JPRESS. Besides, type of head coil, echo time, scan time also play different roles in MRS evaluation [124–126]. These various setting may bring difference of the evaluation results and the problem of reproductivity and false positive [122]. Therefore, considering the reliability of measurement and its determining factor is essential. In particular, there are few related literatures on substance dependence.

6.2 Exploration of other spectroscopy methods

1H-MRS is a common method for neurometabolites detecting. In addition to 1H-MRS, 13C- and 31P-MRS also been used to measure the brain metabolites in substance dependence area. 13C-MRS detects the activity of 13C atoms of labeled precursors (e.g., [1-13C] glucose) in the tricarboxylic acid (TCA) and glutamate-glutamine cycles [127]. Meanwhile, 13C-MRS provides information with respect to the glial-neuronal interactions, especially the glutamatergic function [128]. It is known that there are many interactions between neurons and glial cells, and glutamate neurotransmission is closely related to glucose metabolism [129, 130]. Therefore, application of 13C-MRS technology could bring more different dimension of neural activity information than 1H-MRS. 31P-MRS also has a unique test content, which contain metabolites information with regard to the phospholipid metabolism, tissue bioenergetics, and pH. To be more specific, the major peaks in the spectra correspond to phosphomonoesters, phosphodiesters, high-energy phosphates phosphocreatine, inorganic phosphate, and nucleoside triphosphate (e.g., alpha-, beta-, and gamma-type) [23]. By using the new testing method, it will be able to expand the detectable metabolites types and gain a deeper understanding of the metabolite state of the brain.

6.3 Combing different types of brain detection technologies

1H-MRS is mainly used to detect the level of metabolites, but for the molecular neurobiological framework of the brain, it should also include the functional status of the receptor and the biological processes of different neurometabolites. Therefore, it would be rather promising to unite with different technical means. PET could be applied to observe the metabolite biological processes of the brain by using receptors, transporters, storage vesicles, precursors, related enzymes, blood flow and glucose metabolism of related neurotransmitters as imaging agents. This technology may cause radiation, but after measuring the pros and cons, it is still a technology worth developing. On the other hand, with the application of

transcranial magnetic stimulation, the transcranial magnetic stimulation combined with EEG method to reflect GABA receptor function has also become achievable. For example, a TMS-EEG study suggests that the dorsolateral prefrontal cortex excitability and inhibition function are abnormal in patients with depression [131].

6.4 Dynamic neurometabolite detection

1H-MRS reflects the metabolite level at a certain time, but it is difficult to reflect the dynamic transformation process of metabolites. The pathological process of disease is often dynamic. Through fMRI and EEG studies, researchers have identified the dynamic feature of brain in network and electrophysiologic level [132, 133], while studies focus on the neurometabolite point of view are still insufficient. Through the development of dynamic detection of MRS technology, it contributes to further understand about pathogenesis of substance dependence and other neuropsychiatric diseases.

6.5 Advocate the establishment of a global MRS database

Small sample studies have been influenced by many individualizations and uncertainties. This is common in many studies. In order to solve this problem, internationalized or localized genetics, imaging, and electrophysiology databases have been established. However, until now, there are few online databases related to 1H-MRS. The primary way to combine different 1H-MRS research results is still based on meta-analysis. By building a database, researchers can use consistent analysis methods for raw data, as well as more disease-related analysis. More importantly, this makes the results more credible.

7 Conclusion

1H-MRS as a neuroimaging tool now is widely used in clinical brain researches, to measure the metabolites levels in vivo and to understand the mechanism of neuropsychiatric diseases. As for the technique of 1H-MRS, the methodology in these studies was varied, which might cause the inconsistence of the findings. The methodological heterogeneity includes scan-methods (SVS or MRSI), TE parameters (long or short), voxel size and the quantification and post processing methods, such as quantification algorithms and absolute values or ratios. Therefore, in 1H-MRS studies, methods and parameters are vital for the results, and should be carefully chosen, for higher reliability and comparability. It is never too much to emphasize the significance to promote the development of MRS technology.

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