MAGNETIC RESONANCE IMAGING AND SPECTROSCOPY IN THE STUDY IN ADHD SYNDROME: A SHORT REVIEW
Review paper

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Abstract: This short review describes findings on the characterization of attention-deficit/hyperactivity disorder (ADHD) performed with Magnetic Resonance (MR) techniques. Magnetic Resonance Imaging (MRI) is a powerful technique to discriminate different soft tissues in human body and allows morphological studies in symptomatic subjects. Functional Magnetic Resonance Imaging (fMRI) adopts MRI techniques to detect regional changes of cerebral metabolism in response to a specific activation. If brain activation is achieved by means of appropriate drugs fMRI is called pharmacological MRI (phMRI). The most popular fMRI technique utilizes the blood oxygenation level dependent (BOLD) contrast, which is based on the different magnetic properties of oxygenated and deoxygenated blood. fMRI and phMRI are important tools for understanding impairment in cognitive function and brain development in children with ADHD in humans as well as in animal model. We also review recent in vivo Magnetic Resonance Spectroscopy (MRS) studies of neurobehavioral syndromes. In vivo MRS include a number of non-invasive techniques able to detect biochemical information in a localised brain region, in particular the alterations of metabolism in symptomatic subjects. All these techniques reveal morphological and functional differences between normal and ADHD subjects opening new views in comprehension of the mechanisms which are at the basis of this pathology.

1 INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is a chronic neuro-behavioural disease rather common to children of many different communities worldwide (Faraone, 2003). The estimated prevalence is 4-7% in the USA and 1-3% in the EU. Differences in the prevalence among countries are mainly due to the fact that the impact of this disease is not always recognized by the society as a whole and/or in the diagnostic guidelines set by the medical community (Faraone, 2003; Moffitt and Melchior, 2007). The traits of inattention, impulsivity, and motor hyperactivity are a core characteristic of those individuals diagnosed for ADHD.

ADHD is classically considered an executive dysfunction characterized by poor decision-making. In this perspective, relevance is given to a selective impairment in those processes that evaluate pros and cons in terms of costs and benefits, leading to a choice among alternative possibilities. Alternatively, ADHD can be viewed as a motivational dysfunction, resulting from altered processing of reward value along the fronto-striatal circuits, characterized by efforts to escape or avoid any situation that requires waiting time, slow gathering of information, withholding of impulses, prolonged focusing of attention, etc. (Puumala, 1996; Sadile, 1996; Bolanos, 2003; Sagvolden and Larsen, 1993). ADHD does not lead to positive life outcome. When non-pharmacological, psychotherapy-based approaches do not success, and psychotherapeutic drugs are prescribed to treat evident ADHD symptoms, a clear benefit derives from the treatment. Methylphenidate (MPH), much better known as Ritalin, and atomoxetine (ATM), also known as Strattera, are commonly prescribed to children and adolescents for the treatment of ADHD (Accardo and Blondis, 2001; Levin and Kleber, 1995; Scheffler, 2007). MPH is mainly considered as a dopaminergic agent. However, its pharmacology suggests effects on both neurotransmitters dopamine (DA) and noradrenaline (NA) (Nandam, 2011). Indeed, MPH increases the levels of DA and NA in the brain through reuptake inhibition of the monoamine transporters. On the contrary, ATM is a noradrenaline (NA) reuptake inhibitor. Pharmacological work in rodents has shown that, although ATM selectively inhibits the noradrenaline transporter in prefrontal cortex, there is a resultant threefold increase in both NA and DA levels (Bymaster, 2002). Therefore, although ATM and MPH have similar effects on both DA and NA in prefrontal cortex, a key difference is conferred by the ability of MPH to selectively increase DA within the striatum (Bymaster, 2002). These pharmacological treatments are effective in the management of ADHD symptoms, including cognitive impulsivity (Seeman and Madras, 1998). However, some concern may raise in treating children with a less severe symptomatology, at least in terms of benefit-cost analysis. Indeed, MPH is psychostimulant drug and its pharmacological pathways and psychotropic effects are similar, although not identical, to those targeted by amphetamine and cocaine (Challman and Lipsky, 2002) (Kallman and Isaac, 1975; Patrick and Markowitz, 1997).

In the last years, an increasing amount of data in animal models provided evidence for enduring neuro-behavioural effects of adolescent MPH (Burton and Fletcher, 2010). These persistent and long-lasting consequences, still evident at adulthood, can be beneficial and of great value for ADHD therapy, as is the case for the long-term modulation of self-control abilities. However, there are also examples of detrimental MPH-induced changes. Exposure to MPH at an adolescent age has been reported to modify emotional and motivational responses later in life, whereby MPH leads to decreased sensitivity to rewarding stimuli (Brandon, 2001; Andersen, 2002), enhanced emotionality and depressive-like symptoms (Carlezon and Andersen, 2003; Bolanos, 2003). Magnetic resonance (MR) offers different approaches to study the mechanisms which are at the basis of this pathology. The use of structural (morphological) and functional magnetic resonance imaging (MRI) can detect brain abnormalities both in children and in adults. Moreover magnetic resonance spectroscopy (MRS) is a powerful, non-invasive tool for monitoring the metabolism of neurological diseases in specific brain. In the present paper we will give an overview of the main published works in which the use of MR techniques contributes to a better comprehension of ADHD syndrome.

2 STRUCTURAL MRI

Since its first in vivo application in the 1970s MRI has become one of the main diagnostic tools in brain clinical studies. The major characteristic is the capability to discriminate between soft tissues on the basis of their different magnetic properties. In fact biological tissues have typical MR characteristics called T1 and T2, parameters related to the return to equilibrium after a radiofrequency perturbation which is different for each tissue. In brain studies it is possible to obtain detailed anatomical images by settings proper sequence parameters (for further

Table 1: Structural studies on symptomatic subjects of different age.

Brain Region	ADHD Children	ADHD Adults
Anterior cingulated cortex	Volume reduction (Overmeyer, 2001)	No data
Occipital lobe	Pronounced volume (Castellanos, 2002; Durston, 2004)	No data
Frontal lobe	Volume reduction (Durston, 2004; Hynd, 1990; Castellanos, 1996; Filipek, 1997; Mostofsky, 2002; Hill, 2003; Kates, 2002)	Volume reduction (Hesslinger, 2002)
Temporal lobe	Reduction of the anterior volume (Castellanos, 2002)	No data
Striatum	Volume reduction (pallidum and basal ganglia) (Castellanos, 2002; Castellanos, 1996; Filipek, 1997; Castellanos, 1994; Castellanos, 2001; Castellanos, 2003; Hynd, 1993; Mataro, 1997)	No evidences (Castellanos, 2002)
Corpus callosum	Volume reduction (posterior region mostly affected) (Hill, 2003; Baumgardner, 1996; Giedd, 1994; Lyoo, 1994; Semrud-Clikeman, 1994)	No data
Parietal lobe	Cortical volume increase (Sowell, 2003); Posterior parietal volume reduction (Castellanos, 2002)	No data
Cerebellum	Volume reduction in right hemisphere (Durston, 2004; Castellanos, 1996; Hill, 2003; Castellanos, 2001; Bussing, 2002; Berquin, 1998; Mostofsky, 1998)	No data

details refer to (ed. P.S. Tofts, 2003)). For these reasons morphological MRI has been extensively used in studies on ADHD patients.

MRI detected morphological changes on ADHD patients (adults and children) are presented in table 1. As emerged in the last studies (Emond and Pois11bymastersant, 2009; Schneider, 2006), the volumetric abnormalities involve not only areas know as frontostriatal network (which area predicted by cognitive models of ADHD). Widespread reduction in volume has been observed in total cerebrum and cerebellum.

3 FUNCTIONAL MRI

Functional MRI (fMRI) is a technique for measuring hemodynamic response (change in blood flow and blood oxygenation in the brain) which is related to neural activity in brain. Indeed, when neural cells are activated they increase their consumption of energy from glucose. This consumption causes an increases of blood flow to regions of increased neural activity and leads to local changes in the relative concentration of oxyhemoglobin and deoxyhemoglobin and in local cerebral blood volume and flow.

Several techniques have been developed and utilised to monitor neural activity. One of the most used concerns with the blood-oxygen-level dependence (BOLD) effect which is generated by changes in local ratio of oxyhemoglobin to deoxyhemoglobin. Hemoglobin is diamagnetic when oxygenated (oxyhemoglobin, Hb) but paramagnetic when deoxygenated (deoxyhemoglobin, dHb). In fact, in the dHb, iron has a great magnetic moment because of six external unpaired electrons. Then dHb acts as a contrast agent and it is easily detected. In the Hb, one electron is transferred to oxygen molecule, causing a weaker magnetic moment. The response to the applied fields is different and the MR signal of blood is therefore slightly different depending on the level of oxygenation. The presence of deoxyhemoglobin in a blood vessel causes a susceptibility difference between the vessel and its surrounding tissue. Such susceptibility differences cause dephasing of the MR proton signal, leading to a reduction in the value of T2*. In a T2* weighted imaging experiment, the presence of deoxyhemoglobin in the blood vessels causes a darkening of the image in those voxels containing vessels. Since oxyhemoglobin is diamagnetic and does not produce the same dephasing, changes in oxygenation of the blood can be observed as signal changes in T2* weighted images. It would be expected that due to neural activity, oxygen consumption is increased leading to an increase of the amount of deoxyhemoglobin in the blood, consequently, the MR signal would decrease. Instead, this oxygen consumption is compensated by a rapid arrive

Table 2: Functional studies on symptomatic subjects of different age.

Brain Region	ADHD Children	ADHD Adults
Anterior cingulated cortex	Hypofunctionality (Durston, 2003; Bush, 1999; Rubia, 1999; Zametkin, 1990)	No activation. Compensatory mechanism: activation of frontostrial network using a different region of lateral prefrontal cortex (Oberlin and Marrocco, 2005)
Motor system	Decrease of contralateral motor cortex and right parietal cortex activation (Mostofsky, 2006)	No data
Frontal brain	Reduced brain activation in the right inferior prefrontal cortex (Rubia, 2005). Greater frontal activation, not altered by MPH treatment (Vaidya, 1998)	Activation of the ventral and dorsolateral prefrontal cortex (Ernst, 2003)
Parietal cortex	Low activation of action- attentional system, including superior parietal cortex (Silk, 2005)	No data
Striatum	Reduced activation, restored to normal value by MPH (Vaidya, 1998) Inability to activated caudate nucleus (Vaidya, 2005)	No data

of oxygenated blood in excess which causes an increased of BOLD signal. Although the increase in BOLD signal it is not a direct measure, it is well known its correlation with neural activity. The reasons of negative BOLD signal and their relationship to neural activity are still to be determined. fMRI uses BOLD as contrast for determining where activity occurs in the brain as the result of various experiences or pharmacological stimuli. For further details on the techniques applied in functional and pharmacological MRI, the reader can refer to (ed. S.H. Faro and Mohamed, 2006).

fMRI techniques are useful for studying the impairment of attention networks that, neurologically, can be distinguished into three components:

- the alerting networks: the main function is the activation and synchronization of the cerebral cortex during behaviour and motivation. They involve brain-stem, thalamus and limbic system;

- cortical/subcortical orienting networks, detecting novel stimuli (superior colliculi), filtering out irrelevant stimuli (pulvinar) and disengaging attention focus (posterior parietal cortex);

- selective attentional networks which is particularly interesting in ADHD. This involves frontal brain structure for generation of volitional saccades, induces motor intention (premotor cortex), is linked to working memory (dorsolateral prefrontal cortex) and is modulated by the anterior cingulate cortex. This network is also called the executive network and this has been shown to display high heritability.

Two reviews have summarized the results of several fMRI studies that investigated brain activations related to these three particular aspects of attention in children with ADHD (Emond and Pois11bymastersant, 2009) (Schneider, 2006). Alterations in the neural basis of the two cognitive control operations in childhood suffering of ADHD were also detected by fMRI in medication free children (Vaidya, 2005). Moreover, a controversial study (Vaidya, 1998) showed that methylphenidate (MPH) boosted activity in ADHD children but suppressed in healthy ones. Overall results are summarized in table 2.

4   phMRI

Pharmacological MRI (phMRI) is the application of fMRI to psychopharmacology, where neuronal activation are observed in response to a pharmacological stimulus and it represents a valuable tool in the study of the regional specificity of drug action and the time course over which drugs act. Beside blood oxygenation and blood volume, other physiological parameters such as mean artery blood pressure (MABP) and heart rate (HR) can influence the amplitude and temporal signature of the BOLD signal.

When phMRI is applied to animal models, the stimulation is induced by drugs on anesthetized animals. The role of anesthesia in the BOLD responses is an important issue. A recent study (Greenberg and Kerr, 2008) shows

that the propagation of action potentials changes during the anesthesia. On the other hand, neuronal coupling is reported to be detectable up to 2% isoflurane (Sicard, 2003) although it is reduced compared with that in conscious animals. All these studies highlight the importance of working with awake animals in brain activation imaging studies or to compare only studies with animals under the effect of the same anesthetic compound and anesthesia level.

Several studies on animal models investigated the effect of psychostimulant drugs utilised in the cure of ADHD children. In one study (Canese, 2009), the authors investigate the response of adolescent and adult rats to MPH by using phMRI. Adolescent (post-natal day PND 34 to 43) and adult (PND>60) male rats were treated with MPH (Ritalin, CIBA- GEIGY Spa, Varese, Italy) at a dose of 4mg/kg or saline (control group). The animals were scanned at 4.7 T under the constant supply of anaesthetic gases (isoflurane 1.8% in O2 1L/min). The authors focused their investigation on brain areas that are known to be specifically responsive to psychostimulants: the prefrontal cortex (PFC), the ventral component of the striatal complex (NAcc) and the hippocampus (Hip).
Positive BOLD signal (usually find for cocaine ad amphetamine) was detected as response to the MPH in PFC and NAcc of adult rats, but a widespread decrease of the BOLD signal was found in adolescent brain. In particular, the decrease of BOLD signal occurred earlier in PFC and NAcc than in the Hip (Figure 4).

The negative BOLD signal observed in adolescent rat brains immediately after MPH administration are explained by the authors as the result of an increased oxygen consumption, which is not followed by a prompt hemodynamic response, typical in adult animals. This means that the mechanisms for the feedback reallocation of cerebral blood flow (CBF), following neural activation, are still immature in adolescence. This study raises concerns on the use of psychoactive drugs in children and highlights the importance of using age-matched animal models in the study of drug designed for pediatric population. Another work (Hewitt, 2005) reported a significant BOLD effect in the PFC and NAcc of adult male rats following MPH administration.
Methylphenidate produced a greater locomotor-stimulant response in control rats compared rats pretreated with a dopamine re-uptake inhibitor (GBR 12909, 30 mg/kg i.p).

Pretreatment with GBR 12909 reduced the BOLD response produced by methylphenidate compared with that in control animals. The main effects of methylphenidate on the BOLD response were seen in the caudate, frontal cortex, hippocampus and hypothalamus. Short-term treatment with GBR 12909 in young rats causes long-term changes in dopaminergic systems, altering the methylphenidate-induced behavioral response and brain region activation compared with that in vehicle-pretreated rats. The results further support the view that altered dopaminergic function may be an important factor in ADHD and the value of animal models with this functional neurochemical deficit.

Another study (Easton, 2007) uses phMRI to analyse the response of rats to the atomoxetine, another treatment adopted in ADHD subjects. The phMRI performed at 2.35 T on anesthetized animals treated with atomoxetine (1 ml/kg) or saline (control group) evidenced a negative BOLD signal in the caudate putamen without changes in the NAcc. Other changes were detected in cortico-basal thalamic loop circuits and basal ganglia (which would help to explain the efficacy of atomoxetine in reducing hyperactivity observed in ADHD patients). The authors explain the negative signal as both direct effects of atomoxetine and indirect effects by changes in neurotransmitter levels (as noradrenaline or dopamine) in the microvasculature. The effects observed in this study may reflect some of the early changes in brain region function produced by atomoxetine in human ADHD patients after acute administration.

5 MR SPECTROSCOPY

MRS can measure the in vivo biochemical or metabolite concentration levels in the human body from a specific localized region (Stanley, 2002). Brain is a suitable organ for MRS studies because of its high multiplicity of metabolites and it is not subjected to movement as other organs. It is possible to perform MRS of all the nuclei which has a magnetic momentum. The most biologically relevant nuclei are ^{1}H, ^{31}P and ^{13}C. The chemical-physical principle upon which this technique is based is the chemical-shift i.e. the property of a given element to resonate at a specific resonance frequency depending on the molecular environment which is seen by the element, so different chemical groups within a molecule resonate at different frequencies. The difference between the applied magnetic field B0 and the electronic field due to the environment is expressed as parts per million (ppm) of B0.

The signal-to-noise ratio (SNR) is a very important parameter and much critical for a good and reliable
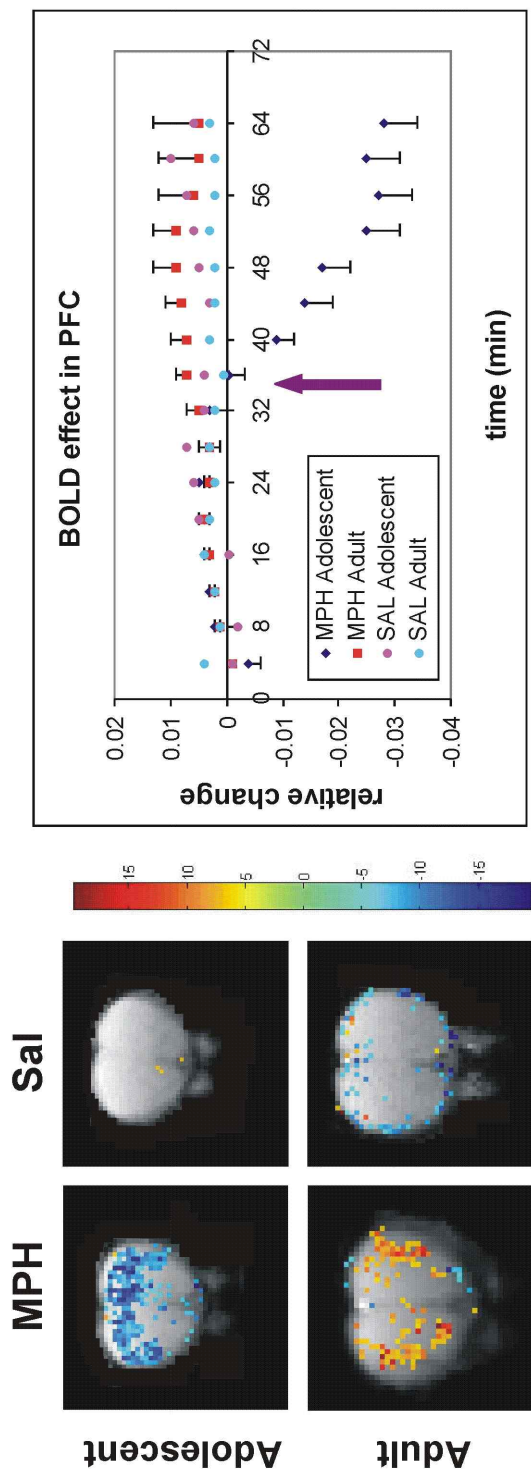
Figure 1.
On the left: BOLD activation maps from rat templates (in color scale) are overlaid on anatomic images (in grey scale) in PFC. Color bar indicates the statistical significance obtained for each pixel of the template. On the right: time courses of the mean signal intensity of adolescent and adults injected with saline (SAL) or MPH (4mg/kg). Reprinted from Canese et al, 2009, Psychopharmacology 203, 143,Äi153. License Number: 26276100642225.

quantification. In general, increasing the magnetic field strength leads to an approximate linear increase in the MR signal amplitude; consequently, leads to smaller localized voxel sizes (that is, greater spatial resolution), which minimizes the degree of partial volume of different tissue types within the localized voxel. Moreover, at higher field strengths, the overlapping among of different peaks is reduced, thus improving the accuracy and precision in quantification of metabolite levels (Hetherington, 1994; Prost, 1997; Bartha, 2002; Bartha, 2002; Tkac, 2001).

^{1}H MRS is also preferred because SNR is proportional to the cube of the gyromagnetic ratio, which is higher for hydrogen. MRS of different nuclei allows detection of different aspects of brain metabolism. ^{1}H MRS enables the detection of several important metabolites, summarized in Table 3 such as glutamate, the g-aminobutyric acid (GABA), N-acetylaspartate (NAA) and myo-inositol (Michaelis, 1993; Frahm, 1989). This information allows to estimate glutamate-glutamine neurotransmission cycling (Coyle, 1997; Tsai and Coyle, 1995) the GABA neuronal system, the viability of neurons (Magistretti and Pellerin, 1999; Rothman, 1999), and the second messenger metabolism, respectively.

Table 3: Table of ^{1}H MR-detectable metabolites (ed. P.S. Tofts, 2003).

Metabolite	Chemical shift (major resonance): normal concentration median(range)	Physiological significance
NAA (N-acetyl-aspartate, other N-acetyl moieties)	2.02 ppm 7.8 mM(6.5-9.7)	Healthy neuronal cell marker. Only seen in nervous tissue. Exact physiological role uncertain.
tCho (Choline-containing compounds)	3.2 ppm 13mM (0.8-1.6)	Detectable resonance is predominantly choline derivates. Marker of the membrane turnover. Higher in white matter than grey matter. Increase with age.
tCr (Creatine + Phospho-creatine	3.0 ppm 4.5 mM (3.4-5.5)	Compounds related to energy storage; thought to be energetic cells. Other metabolites are frequently expressed as ratio to Cr. Low in infants. Increases with age.
Ins (Myo-inositol)	3.56 ppm 3.8 mM (2.2-6.8)	Pentose sugar. Involved inositol triphosphate intracellular second messanger cycle, osmolyte, glial cell marker. High in infants.
Glx (Glutamate, Glu + Glutamine, Gln)	3.77 ppm Glu 10 mM,Gln 5mM	Complex overlapping J-coupled resonances difficult to separate and quantify at clinical field strengths (1.5-3T. Amino acid neurotransmitters Glu excitatory, Gln inhibitory
Lactate	1.33 ppm (doublet 7 Hz separation) Detectable 1mM	Not seen in normal adult brain. End product of anaerobic respiration. May be energetic substrate of much brain metabolism. Thought to be elevated in foamy macrophages.
Lipids (Mobile lipid moieties)	0.9 and 1.3 ppm	Not seen in normal brain. Membrane breakdown/lipid droplet formation. May precede frank histological necrosis.
Tau (taurine)	3.2 and 3.4 ppm	implicated in inhibitory neurotransmission and in long-term potentiation in the striatum/hippocampus; protective against glutamate toxicity; antioxidant and protects against toxicity of various substances.
GABA (γ-aminobutyric acid)	1.9, 2.1 and 3.0 ppm	Major inhibitory neurotransmitter in the mammalian central nervous system.

A limit of ^{1}H MRS is the small spectral range in which all the metabolites resonate. In fact, several resonances for example those of phosphocreatine (PCr) and creatine (Cr) which are important in the high energy phosphate metabolism are overlapped and therefore indistinguishable at low magnetic field, as those used for clinical purposes (Stanley, 2002). A typical ^{1}H spectrum obtained from a rat hippocampus is shown in figure 2.
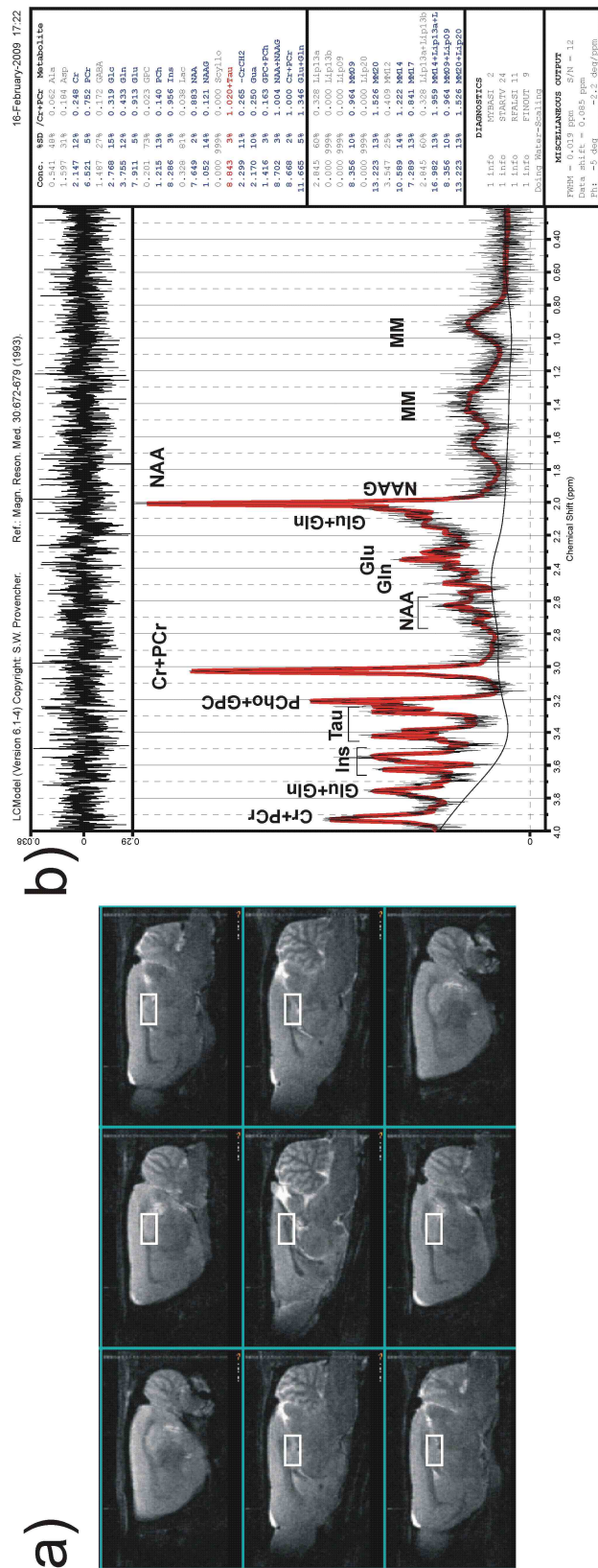
Figure 2

a) Example of in vivo sagittal T2-weighted spin-echo images of rat brain. Voxels localized on Hip is indicated by the white rectangles.

b) Example of in vivo 1H MR spectrum acquired from hippocampus and metabolite quantitative analysis performed by LCModel fitting program.

On the other hand, ^{31}P spectroscopy can measure the metabolite levels of adenosine triphosphate (ATP), PCr, and inorganic orthophosphate (Pi), which are associated with high-energy phosphate metabolism (Bessman and Geiger, 1981; Wallimann, 1992). ^{31}P spectroscopy allows to assess the membrane phospholipid synthesis and degradation measuring the freely mobile water-soluble phosphomonoesters (PME) and phosphodiesters (PDE), respectively (Pettegrew, 1987). In the end, ^{13}C NMR can directly measure glucose oxidation and glutamatergic neurotransmission, thereby providing more direct information about these metabolic processes. Stimulated Acquisition Mode (STEAM) and the Point-Resolved Spectroscopy (PRESS) pulse sequence (Tkac, 2001; Frahm, 1989; Bottomley, 1987) are commonly used in localized ^{1}H MRS. Both these sequences acquire the MR signal from the intersection of 3 orthogonal slices or slabs and can be applied to localize either a single voxel or, combined with phase-encoding gradients, to localize multiple voxels simultaneously in 2 or 3 dimensions. The most used technique in 31P MRS is image-selected in vivo spectroscopy (ISIS). ^{1}H MRS is a very powerful technique to investigate in behavioral syndromes such as ADHD because we can compare the metabolism of brain development in healthy adolescents and in the symptomatic ones. Control study (Horska, 2002) reported the metabolism changes in brain from childhood to adolescence. The study deals with fifteen healthy subjects from three to 19 years old examined by in vivo multivoxel MRS and it finds that the ratio of NAA/Cho in cortical grey matter increased with age until 10 years and then decrease as expected from synaptic pruning during adolescence. On the contrary, the same ratio in white matter increases linearly and this is in agreement with age-related increases in white matter volumes.

A recent meta-analysis reviewed 16 MRS studies of ADHD (Perlov, 2009) considering the measured metabolites and regions of assessment. Two regions were analyzed: the basal ganglia, mostly striatum, and the frontal lobes of ADHD and normal children. In particular the tCho, NAA and Glx related to tCr signal were found to be altered in several studies in ADHD patients. Moreover, tCho increased in the investigated regions. Methodological improvements of MRS are desirable in order to evaluate the absolute concentrations rather than ratios and standardized protocols in order to compare data acquired in different centre. In a recent study on ADHD Yang and colleagues (Yang, 2010) analyzed, by a quantitative approach, the prefrontal area of adolescent brains using short echo time ^{1}H MRS. They found a reduction in tCr level in the right prefrontal cortex. This finding provides evidence of a prefrontal neurochemical alteration in the adolescents' ADHD mechanism.

In the literature, several studies on animal models of ADHD are also described. Using MRS Adriani et al. (Adriani, 2007) characterize the metabolic long-term brain changes in adult rats induced by exposition to MPH during adolescence. This work joins impulsivity test and a quantitative MRS analysis on two different rat groups, the MPH exposed rats and saline exposed rats (the control group). tCr and Tau, metabolites respectively involved in bioenergetics and synaptic efficiency, were up-regulated in the STR and conversely down-regulated in the NAcc of MPH exposed rats. Unaltered tCr and increased PCr/tCr ratio were detected in the PFC. These findings highlight the role of these metabolites in the regulation of impulsivity in rats. Another study (Adriani, 2010) investigates the same brain regions in animals inoculated in NAcc with a lentiviral vector that modulates the expression of the gene responsible of the synthesis of the protein DAT (a dopamine transporter) in different ways. Four groups were considered: control group, silencers (SIL), and enhancers (DAT+) and (DAT+SIL). The aim of this work was to understand the role of dopamine in the impulsive behavior. Changes among groups were detected mainly in STR and NAcc on bioenergetic metabolites (tCr and PCr) and were related to specific animal behavior.

6   CONCLUSIONS

The complexity of the ADHD syndrome that causes both executive and motivational dysfunction needs a full characterization in order to cover all the variety of symptoms. The overall body of the studies reviewed here show that the use of morphological and functional MRI together with metabolic assessment in specific brain areas by localized MRS may substantially improve the diagnosis and the characterization of ADHD. Moreover, longitudinal studies can be performed and the effects of conventional and innovative therapies can be monitored making MRI and MRS fundamental investigative tools in the study of ADHD.

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