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GABAergic contributions to alcohol responsivity during adolescence: Insights from preclinical and clinical studies

Marisa M. Silveri *

Neurodevelopmental Laboratory on Addictions and Mental Health, McLean Hospital, Belmont, MA, USA
Department of Psychiatry, Harvard Medical School, Boston, MA, USA

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ABSTRACT

There is a considerable body of literature demonstrating that adolescence is a unique age period, which includes rapid and dramatic maturation of behavioral, cognitive, hormonal and neurobiological systems. Most notably, adolescence is also a period of unique responsiveness to alcohol effects, with both hyposensitivity and hypersensitivity observed to the various effects of alcohol. Multiple neurotransmitter systems are undergoing fine-tuning during this critical period of brain development, including those that contribute to the rewarding effects of drugs of abuse. The role of developmental maturation of the γ-amino-butyric acid (GABA) system, however, has received less attention in contributing to age-specific alcohol sensitivities. This review integrates GABA findings from human magnetic resonance spectroscopy studies as they may translate to understanding adolescent-specific responsiveness to alcohol effects. Better understanding of the vulnerability of the GABA system both during adolescent development, and in psychiatric conditions that include alcohol dependence, could point to a putative mechanism, boosting brain GABA, that may have increased effectiveness for treating alcohol use disorders.

Contents

1. Introduction

Alcohol use is typically initiated during the period of adolescence in humans (Bates & Labouvie, 1997; Hingson et al., 2006a), a critical age span that overlaps with significant brain maturational processes that make the adolescent brain more vulnerable to alcohol exposure than their more "neurobiologically adult" counterparts (Clark et al., 2008; Bava & Tapert, 2010; Blakemore, 2012). There are several behavioral features associated with adolescence, including but not limited to increased impulsiveness and risk taking, and suboptimal decision-making skills, which could contribute to increased vulnerabilities for developing heavy alcohol and drug use (Tapert & Schweinsburg, 2005; Nixon & McClain, 2010; Spear, 2011a) or early manifestation of

Abbreviations: ACC, anterior cingulate cortex; ALC, alcohol; AUD, alcohol use disorder; CIE, chronic intermittent ethanol; DLPFC, dorsolateral PFC; fMRI, functional magnetic resonance imaging; GABA, γ amino-butyric acid; GAD, glutamic acid decarboxylase; GM, gray matter; IPSPs, inhibitory postsynaptic potentials; LORR, loss of the righting response; LTP, long-term potentiation; MR, magnetic resonance; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; MTL, medial temporal lobe; NMDA, N-methyl-D-aspartate; OCC, occipital cortex; P, postnatal day; PET, positron emission tomography; PFC, prefrontal cortex; POC, parieto-occipital cortex; PTZ, pentylenetetrazole; RORR, regain of the righting response; SPECT, single photon emission computed tomography; tDCS, transcranial direct current stimulation; WM, white matter.

* McLean Imaging Center, McLean Hospital, 115 Mill St., Mailstop 204, Belmont, MA 02478, USA. Tel.: 617 855 2920; fax: 617 855 2770.
E-mail address: msilveri@mclean.harvard.edu.

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psychiatric illnesses (Paus et al., 2008; Gogtay & Thompson, 2010) during this age span. These behavioral features have neurobiological underpinnings that include structural, functional and neurochemical developmental brain changes that are unique to adolescence, that are particularly prominent in the frontal lobe and that are commensurate with developmental improvements in executive functioning skills (Gogtay et al., 2004; Casey et al., 2005). These features observed in adolescents overlap with similar features observed in cohorts of adult patients with alcohol use disorders and psychiatric illnesses, namely risk-taking, impulsiveness, and differences in brain tissue volume, functional brain activation and neurochemistry. This overlap collectively highlights the vulnerability of the adolescent brain to the early manifestation of addictive disorders and psychiatric conditions. Accordingly, characterizing the ontogeny of multiple neurotransmitter systems has been the subject of numerous investigations (for review, see (Spear, 2000), however more recently, investigation into the development of the inhibitory neural system, γ-amino-butyric acid (GABA), is gaining significant attention as a potential moderator of human developmental changes in impulse control, self-regulation and decision-making (Silveri et al., 2013). Parallel to studies investigating contributions of brain GABA to functioning during adolescence is an accumulation of GABA findings based on studies conducted in healthy adults (Northoff et al., 2007; Boy et al., 2010; Goto et al., 2010; Sumner et al., 2010; Stagg, 2014) and in adult patients with psychiatric illnesses (Streeter et al., 2005; Ham et al., 2007; Bhagwagar et al., 2008; Pollack et al., 2008; Yoon et al., 2010; Plante et al., 2012a; Simpson et al., 2012; Long et al., 2013; Rosso et al., 2014). Notably, the role of GABA in alcohol responsiveness has been well established in animal models, and GABA-related alterations have been investigated in humans with alcohol use disorders (Behar et al., 1999; Mason et al., 2006; Abe et al., 2013; Mon et al., 2012; Silveri et al., 2014). Together these studies implicate *in vivo* brain GABA alterations in disease symptomatologies, particularly in alcohol dependence, alcoholism vulnerability, and pharmacotherapies available for treating alcoholism (Krystal et al., 2006) (Fig. 1).

Examples are provided that span domains of motor control, anxiety, and cognition, which permit an opportunity to draw parallels between preclinical studies of adolescent-specific responsiveness to alcohol and clinical studies of brain GABA levels, with a goal of inspiring novel lines of research investigations in alcohol abuse research.

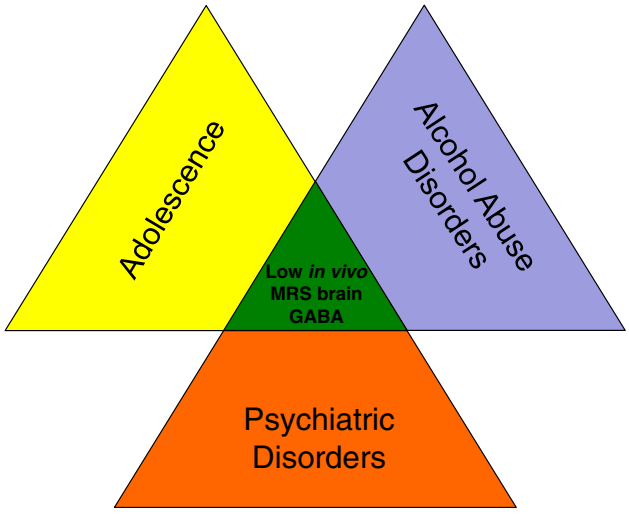

Fig. 1. Schematic highlighting the overlap of low brain GABA levels measured using MRS in adolescents, adults with alcohol use disorders and adults with psychiatric disorders (e.g., major depressive disorder and anxiety disorders).

2. Setting the stage

2.1. Epidemiology of adolescent alcohol use

Excessive alcohol consumption is the third leading cause of preventable death in the United States (Mokdad et al., 2004). The onset of alcohol use frequently occurs during adolescence, increasing in prevalence of use from 3% at age 12 to 68% at age 21 (SAMHSA, 2010a). As prevalence of use increases with age, drinking patterns and quantity of alcohol consumed likewise increase. A recent national survey indicated that 508,329 adolescents aged 12–17 years drank alcohol on at least one day during the past year, averaging 4.6 drinks consumed per day of drinking (SAMHSA, 2010b). Thus, patterns of alcohol drinking often reach heavy episodic, or binge-like levels during adolescence. Binge drinking is generally defined as a pattern of drinking that raises blood alcohols levels to 0.08 g% or greater over a two-hour period, which typically translates to 5+ drinks for adult men and 4+ drinks for adult women (NIAAA, 2004). In adolescents, 7% of 8th graders, 16% of 10th graders, and 23% of 12th graders reported having drank 5+ drinks in a row within the two weeks prior to survey completion (Johnston et al., 2011). Furthermore, prevalence of alcohol dependence in adulthood is strongly influenced by age of first alcohol use: there is a 38.0% chance of developing alcohol dependence later in life if drinking onset occurs before age 15. Importantly, the rate of prevalence (likelihood) subsequently decreases with each year that the onset of alcohol consumption is delayed during adolescence, falling to ~10% (but not zero) if individuals wait until the legal age to drink in the United States (21 years old) (Grant & Dawson, 1997; Hingson et al., 2006b).

2.2. Adolescent brain development: focus on γ-amino-butyric acid (GABA)

The age of onset of alcohol use, the rapid escalation in alcohol consumption, and the high prevalence of alcohol use disorders (AUD) co-occur during the critical period of adolescent brain maturation and refinement. Thus, identifying neurodevelopmental vulnerabilities associated with early and escalating alcohol use, particularly during adolescence, is critical (Casey & Jones, 2010). Adolescence in humans is typically defined as ages 9 to 18 years of age (Buchanan et al., 1992; Hollenstein & Lougheed, 2013), although more recent neuroimaging studies have begun to redefine the completion of adolescence based on reaching a plateau in structural brain development, which spans the entire second decade and into the early twenties (Gogtay et al., 2004; Bennett & Baird, 2006; Giedd, 2008), or the period of "emerging adulthood". The term emerging adulthood has been ascribed to ages 18–25 years (Arnett, 2000), the late adolescent period that overlaps with the final stages of brain maturation (Gogtay et al., 2004; Bennett & Baird, 2006), in which individuals are functionally more independent than adolescents, but not as independent as individuals aged 25 and older (Arnett, 2001). In order to provide species-specific context for integrating findings across preclinical and clinical studies presented in this review, age spans of adolescence and emerging adulthood as defined in humans roughly correspond in rats to postnatal (P) days 28 to 42 for adolescence (Spear, 2000) and P42 to 55 for late adolescence/"emerging adulthood" (Vetter-O'Hagen & Spear, 2012), in mice from P23 to 35 for pre-adolescence and P36 to 48 for mid adolescence (Adriani et al., 2004), in cats adolescence is around 11 weeks (Chen et al., 2007), and in non-human primates adolescence lasts roughly from two to four years (Schwandt et al., 2007).

Adolescent structural and functional maturational brain changes have been well-characterized (Spear, 2000; Paus, 2005), due in part to the increasing availability of non-invasive magnetic resonance (MR) techniques. Consistent with physiological and social maturation from adolescence through emerging adulthood, developmental changes in white matter (WM) and gray matter (GM) tissue volumes have been observed throughout the second decade of life, i.e., adolescence (Pfefferbaum et al., 1994a; Giedd et al., 1996a, 1999a; Sowell et al.,

2001, 2004; Nagel et al., 2006; Herting et al., 2012), with WM alterations generally reflecting axon myelination and GM changes reflecting pruning and elimination of synaptic connections (Casey et al., 2005). Significant longitudinal structural changes, including increased cerebral spinal fluid and GM reductions in frontal and parietal brain regions, have even been detected in as small as a 7-month window during adolescence, suggesting that maturational changes during this age span occur in a very rapid fashion (Sullivan et al., 2011). Simultaneously, there are dramatic improvements in higher order cognitive abilities (e.g., executive functions) that occur towards the end of the adolescent period and into emerging adulthood (Williams et al., 1999; Anderson, 2001; Klenberg et al., 2001; Rosso et al., 2004), which are related to a marked, later reorganization and refinement of the frontal lobe and to improved functional WM connectivity within and between brain cortical and subcortical brain regions (Pfefferbaum et al., 1994b; Giedd et al., 1999b; Casey et al., 2000; Sowell et al., 2001, 2004). In addition to these cognitive improvements during adolescence, there is also an increased propensity to seek out novel stimulation and engage in risk-taking behaviors during this time (Arnett, 1992; Trimpop et al., 1999), likely related to immature cognitive and behavioral response inhibition abilities. Accordingly, functional magnetic resonance imaging (fMRI) studies document significant increases in the magnitude of frontal lobe activity during the performance of executive function tasks, highlighting the importance of maturation of this region in contributing to age-related improvements in self-regulatory control (Dempster, 1992; Casey et al., 2000; Schweinsburg et al., 2004; Durston et al., 2006; Silveri et al., 2011). There has been a paucity of studies utilizing magnetic resonance spectroscopy (MRS) to measure brain chemistry during healthy development (Cohen-Gilbert et al., 2014), however, with only one published study documenting significantly lower GABA levels in the anterior cingulate cortex (ACC) region of the frontal lobe, but not in the parieto-occipital cortex (POC) of healthy adolescents compared to emerging adults (Silveri et al., 2013) (Fig. 2).

While the frontal cortex undergoes the most substantial structural and functional maturation during adolescence, age-related changes in the medial temporal lobe (specifically, the amygdala and hippocampus) have likewise been reported (Giedd et al., 1996b; Sowell & Jernigan, 1998; Suzuki et al., 2005; Gogtay et al., 2006; Demaster & Ghetti, 2013; Uematsu et al., 2012). Taken together, adolescent maturational brain changes occurring in important brain regions, the frontal lobe and the hippocampus, continue well into emerging adulthood. Not only are these regions, and their associated functions, the last to reach adult levels (Gogtay et al., 2004, 2006), these regions are also the first to deteriorate in healthy aging (Raz et al., 2005, 2007), and both are particularly susceptible to the negative consequences of alcohol consumption (Oscar-Berman & Ellis, 1987; Oscar-Berman & Marinkovic, 2007).

On a neural level, refinement of multiple neurotransmitter systems contribute to the overarching structural and functional brain changes observed during adolescence (Spear, 2000), with developmental refinement of the GABA system in particular being linked to changes in cortical-related activity (Vincent et al., 1995; Tseng & O'Donnell, 2007; Cunningham et al., 2008; O'Donnell, 2012). Such GABA changes include enhanced inhibition, which on a behavioral level likely serves to improve self-regulatory control. The following sections describe an abundant preclinical literature across several species (rats, mice, cats, and monkeys) that is continuing to expand regarding the maturation of this main inhibitory neurotransmitter in the mammalian brain (McCormick, 1989). Indeed, developmental maturational changes in GABA occur across many cellular domains, including changes in GABA concentration, synthesis, turnover, and transport, density of GABA receptors, GABA receptor subunit compositions, and GABAergic post synaptic responses (for review, see Kilb, 2012), as described below.

At birth, on a macroscopic level, whole brain GABA concentrations in rodents are approximately 50% of adult levels (Coyle & Enna, 1976). Levels of glutamic acid decarboxylase (GAD), responsible for synthesis of GABA via decarboxylation of glutamate to GABA and carbon dioxide, increase at a slower rate ontogenetically than GABA concentrations (Coyle & Enna, 1976; Johnston & Coyle, 1981). There are two isoforms of GAD, GAD67 mainly catalyzes cytoplasmic GABA pools and GAD65 predominantly catalyzes synaptically directed GABA (Soghomonian &

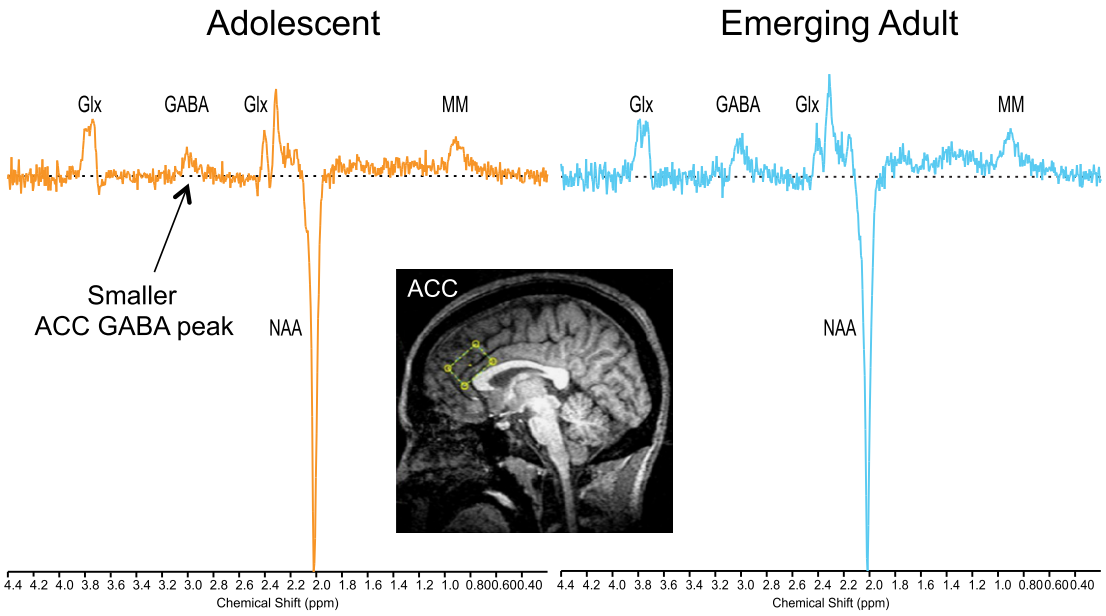

Fig. 2. Sample raw MRS spectral data were acquired at 4.0 T using MEGAPRESS from the anterior cingulate cortex (ACC, sagittal image insert depicting ACC voxel placement) from an adolescent (orange, left spectrum) and an emerging adult (blue, right spectrum). A smaller ACC GABA peak is evident in the sample adolescent difference-edited MEGAPRESS spectrum compared to the sample from the emerging adult. When the GABA peak was quantified and normalized to creatine for each subject and averaged for each age group, significantly lower ACC brain GABA levels (22.6%, $p = .029$) were evident in $n = 30$ adolescents (age range: 12–14 years, average: 13.6 ± 0.9 (SD) years) compared to $n = 19$ emerging adults (age range: 18–24 years, average: 21.6 ± 1.7 (SD) years). See also (Silveri et al., 2013).

Martin, 1998). In cat visual cortex, levels of GAD67 are detectable at birth and reach adult levels early in life, whereas maturation of GAD65 continues into adolescence (Guo et al., 1997). To the extent that GABA plays a number of prominent roles in addition to inhibitory neurotransmission, including metabolism of glucose and fatty acids, GABA concentrations are likely a liberal index of GABA development as compared to enzymatic activity or density of receptors (Coyle & Enna, 1976).

In presynaptic endings, vesicular GABA transporters (VGAT) do not exhibit major developmental changes, whereas plasmalemmal GABA transporters (GAT-1,2,3) located in neurons, glial cells and leptomeningeal cells are typically low at birth in neonatal rat and postmortem human brain, become overexpressed during adolescence and then decline to adult levels (GAT-1) (Xia et al., 1993) or are high at birth and up-regulated to reach adult levels during adolescence in rat cerebral cortex (GAT-2,3) (Minelli et al., 2003). Levels of GAT-1 influence presynaptic uptake and shorten GABAergic postsynaptic potentials, however it is noteworthy that GABA-degrading enzymes, e.g., GABA-transminase (GABA-T), increase to reach adult levels in rats during adolescence (Pitts & Quick, 1967; Kristt & Waldman, 1986), suggesting that adolescent-related modulation of GABA transporters and turnover both contribute to the maturation of GABA neurotransmission.

In the cortex, there are three classes of GABA interneurons, which are categorized based on morphological characteristics, basket (nest, small and large) cells, Chandelier, and Martinotti cells, whereas in the hippocampus, 21 classes of GABA interneurons have been identified (Kilb, 2012). Across these various interneuron cell types, GABAergic interneurons throughout the neocortex undergo massive modifications, in which some interneurons increase linearly to reach adult density after adolescence in monkeys (large basket cells, Erickson & Lewis, 2002), whereas other types of interneurons increase dramatically in density, are transiently overexpressed during adolescence, and are then pruned to adult levels (Chandelier and Martinotti cells) (in monkeys, Anderson et al., 1995; Cruz et al., 2003; in cats, Wahle, 1993). In a human post mortem study, mRNA expression of seven calcium binding proteins and neuropeptides expressed by GABAergic interneurons were examined in the dorsolateral PFC (DLPFC) of individuals from age 6 weeks to 49 years (Fung et al., 2010). Expression of parvalbumin (Chandelier and basket cells) and cholecystokinin (large basket cells) demonstrate a delayed increase, with levels peaking during the adolescent years, whereas other calcium binding proteins or neuropeptide expression either peak earlier in development or decrease slowly over the age span examined (in humans, Fung et al., 2010; in rats, Kawaguchi & Kondo, 2002). In contrast, GABA interneurons in the hippocampus generally have been found to obtain adult morphological characteristics early in life, prior to adolescence (in mice, Jiang et al., 2001). These developmental changes in GABA interneurons, some of which span, peak or end prior to adolescence, suggest that inhibitory input undergoes considerable refinement prior to adulthood, which can not only influence age-typical improvements in behavior (reduced impulsivity) and cognition (executive functioning, including response inhibition), but also mediate age differences in the responsivity to alcohol effects. However, ontogenetic changes in the GABAergic system that coincide with the adolescent period are considerably more complex than the contributions of GABA interneuron receptor density alone.

Synaptic effects of GABA are mediated through two major receptor subtypes, $GABA_A$ and $GABA_B$ receptors. $GABA_A$ receptors are ionotropic heteropentameric membrane proteins that are assembled from 19 receptor subunits: α_{1-6}, β_{1-6}, γ_{1-3}, δ, ε, θ, π, and ρ_{1-3} (Sieghart & Sperk, 2002; Olsen & Sieghart, 2008). $GABA_B$ receptors are metabotropic heterodimers that consist of two receptor subunits: GABR1 and GABR2. $GABA_A$ receptors rise sharply though the early adolescent period in rats (Candy & Martin, 1979), with expression and function of $GABA_A$ receptors differing more dramatically during development than $GABA_B$ receptors (Henschel et al., 2008). In non-human primates, $GABA_A$ receptor density is transiently up-regulated, reaches peak levels during the onset of adolescence and then slowly declines to reach adult levels (Lidow et al., 1991). The ontogeny of $GABA_A$ binding is more pronounced in humans, because the density of GABAergic receptors increases fivefold around birth and then an additional 100% increase that lasts for the following several weeks (Brooksbank et al., 1981). Furthermore, data from human studies have shown that while $GABA_A$ receptors in subcortical structures (e.g., basal ganglia) reach adult-like levels early during adolescence (~14 years), $GABA_A$ receptors reach adult-like levels by 18 years of age in the frontal cortex and by 19.5 years of age in the PFC (Chugani et al., 2001). While there is evidence for developmental changes in $GABA_B$ receptors, rodent studies suggest that $GABA_B$ receptors are functional within the first three postnatal weeks, with little evidence for subsequent changes into adulthood (Kilb, 2012). Given that $GABA_B$ receptors likely undergo minimal developmental changes during adolescence, this review focuses on the putative role of $GABA_A$ receptors in the observed adolescent-specific sensitivity to alcohol. Although it is of note that a growing number of studies provide evidence for a role of the $GABA_B$ receptor in regulating alcohol sensitivity via GABAergic synapses (Ariwodola & Weiner, 2004; Wu et al., 2005), and that treatment with the $GABA_B$ receptor agonist baclofen has shown some promise in the treatment of alcoholism in humans (Colombo et al., 2004; Addolorato et al., 2009).

There are several binding sites on the $GABA_A$ receptor, including binding sites for endogenous GABA and exogenous GABA agonists and antagonists, muscimol, gaboxadol, and bicuculline (Henschel et al., 2008; Sigel & Steinmann, 2012). The $GABA_A$ receptor also contains several allosteric binding sites, which provide indirect modulation of the receptor. The following positive allosteric modulators indirectly promote GABA action: benzodiazepines, nonbenzodiazepines (e.g., zolpidem), barbiturates, ethanol, some neuroactive steroids, e.g., allopregnanolone, progesterone derivatives 3α-hydroxy-5α-pregnan-20-one (3α,5α-THP) and 3α,21-dihydroxy-5α-pregnan-20-one (THDOC), and anaesthetics (e.g., propofol) (Sigel & Steinmann, 2012). The following negative allosteric modulators indirectly reduce GABA action: flumazenil, Ro15-4513 and some neurosteroids (e.g., dehydroepiandrosterone (DHEA) and DHEA sulfate, pregnenolone and pregnenolone sulfate). GABA neurotransmission can also be inhibited by the non-competitive antagonist picrotoxin, which binds to or near the pore of the GABA receptor and directly blocks chloride (Cl^-) from flowing through the channel, which would subsequently lead to depolarization of the cell membrane (Henschel et al., 2008; Sigel & Steinmann, 2012).

The binding affinity of $GABA_A$ receptor sites, channel conductance and other physiological properties of the $GABA_A$ receptor are determined by composition of receptor subunits. While there is a multitude of possible isoforms than can result from the 19 available $GABA_A$ receptor subunits, only a restricted number of subunit combinations are observed in brain (Farrant & Kaila, 2007). The minimal requirements to produce a GABA-gated ion channel are inclusion of α and β subunits, and an additional γ or δ subunit. The $\alpha_1\beta_2\gamma_2$ combination is the most abundant, followed by $\alpha_2\beta_3\gamma_2$ and $\alpha_3\beta_3\gamma_2$, and in some $GABA_A$ receptors, the γ subunit is replaced by δ, ε, or π, and the β subunit is replaced by θ (Henschel et al., 2008). $GABA_A$ receptors are localized to both postsynaptic and extrasynaptic sites. Postsynaptic receptors mediate phasic inhibition via the release of GABA, an opening of $GABA_A$ Cl^- channels, and ultimately, hyperpolarization of a depolarized membrane. In contrast, extrasynaptic receptors mediate tonic inhibition via responsiveness to low ambient GABA levels that increase the length of time the $GABA_A$ receptor is open (Sigel & Steinmann, 2012). The δ subunit in particular is only found on extrasynaptic $GABA_A$ receptors (Farrant & Nusser, 2005; Kilb, 2012). Importantly, it is the composition and arrangement of subunits that determines the functional and pharmacological diversity of $GABA_A$ receptors (Minier & Sigel, 2004; Olsen & Sieghart, 2009), including responsiveness to the presence of alcohol (Faingold et al., 1998; Kumar et al., 2009).

From a developmental perspective, $GABA_A$ receptor subunits undergo significant spatial and temporal maturational changes, supporting that expression and function of $GABA_A$ receptors during development

that differs from adults (Henschel et al., 2008; Kilb, 2012). The most notable developmental changes in $GABA_A$ receptor subunits have been reported for α_1, α_2, α_5, β_2, γ_2, and δ subunits. In rodent and human studies, expression and regional distribution of the α_1 subunit is low at birth but is up-regulated during the early postnatal period, peaking from P21 to 28 and then declining by 20% to reach adult levels at P60 (Gambarana et al., 1991; Santerre et al., 2013). In contrast, the α_2 subunit is more widely distributed at birth and is either constant or declines until adulthood (Laurie et al., 1992), although α_2 subunits are replaced by α_1 subunits (Fritschy et al., 1994). Levels of α_3 are highly expressed in frontal and perirhinal cortex, and are up-regulated during from P10 to P30 (Yu et al., 2006), whereas the α_5 subunit demonstrates a pronounced down-regulation from P30 to P60 (Laurie et al., 1992). While β_1 has a limited distribution throughout the brain and is constant throughout development, β_2 and β_3 are more widely distributed and increase predominantly from P14 to P21, continuing to increase to reach adult levels by P60 (Gambarana et al., 1991). In contrast, the γ_2 subunit peaks from P14 to P21, but then decreases to reach adult levels by P60 (Gambarana et al., 1991). Lower δ subunit expression in cortex has also recently been reported in adolescents (P28–42) relative to adults (P75) (Santerre et al., 2013). There are important developmental patterns of subunit expression that are regionally-dependent, such as in the hippocampus, where developmental expression patterns are opposite from those observed in cortex, e.g., in hippocampus α_1 subunits are down-regulated, and α_2 and α_5 subunits are up-regulated (Laurie et al., 1992; Yu et al., 2006). In the cerebellum, α_1 subunits are also down-regulated, as opposed to the pattern of up-regulation observed in cortex. Similarly, γ_2, β_2, β_3 and δ subunits in the cerebellum are down-regulated throughout development, whereas α_6 subunits, which are only expressed in cerebellum, are up-regulated into adulthood (Gutierrez et al., 1997). Given that the composition and arrangement of $GABA_A$ receptor subunits determines responsiveness to drugs, including alcohol, developmental changes in $GABA_A$ receptor subunits are a putative mechanism underlying the unique responsiveness of adolescents to alcohol effects relative to adults.

In contrast, the glutamate system, the main excitatory neurotransmitter in brain, and the glutamate type receptor, N-methyl-D-aspartate (NMDA), undergo a somewhat opposite profile of maturational changes during ontogeny. Unlike the slower maturation of GABA receptor density, changes in enzymatic activity, and receptor subunit composition, data from previous rodent studies have shown that there is a transient peak in glutamate activity around 2–3 weeks postnatally (Saransaari & Oja, 1995), and that the density of NMDA receptor sites increases dramatically from postnatal day (P)14 until P21 in rats, and then decreasing to reach adult levels (Pruss, 1993). The transient overexpression of NMDA receptors in a number of brain regions early in ontogeny may be critical for synaptic plasticity, as well as related to an increased susceptibility of young animals to NMDA neurotoxicity (McDonald & Johnston, 1990). A trend for higher *in vivo* ACC glutamate levels was also observed in human adolescents compared to emerging adults, measured using proton MRS (Silveri et al., 2013).

Although beyond the scope of this review, neurotransmitter systems other than GABA and glutamate undergo significant developmental changes during adolescence that likely influence responsiveness to alcohol and other drugs of abuse, including but not limited to the dopamine system (Andersen et al., 2002; Brenhouse et al., 2008; Chen et al., 2010; Brenhouse & Andersen, 2011). To date, non-invasive MRS methods for detecting *in vivo* neurotransmitter levels are limited to GABA and glutamate, but as neuroimaging methods continue to evolve, perhaps one-day non-invasive detection of *in vivo* dopamine and other neurotransmitter levels will be possible. Nonetheless, longitudinal *in vivo* studies of neurochemical changes in healthy adolescents are needed to characterize the maturational profiles of GABA and glutamate throughout the course of adolescent brain development, as such data are sorely lacking, along with neurotransmitter-related improvements in cognitive functioning and changes in other behavioral features of adolescence. Furthermore, determining developmental profiles of these opposing neural systems would significantly advance our understanding of neurochemical correlates associated with underage alcohol consumption (Silveri, 2012).

2.3. Brain alterations associated with alcohol use disorders

Heavy alcohol consumption has been associated with deficits across several domains of cognition in adults (Oscar-Berman, 1990, 2000; Parsons & Nixon, 1998; Oscar-Berman & Marinkovic, 2003), with executive functioning and memory domains most vulnerable to disruptions by alcohol (Oscar-Berman & Ellis, 1987; Oscar-Berman & Marinkovic, 2007). Cognitive impairments have been demonstrated under conditions of acute alcohol challenges, in non-drinkers and drinkers, and in populations of binge drinkers, chronic heavy drinkers, alcohol dependent and recently abstinent alcohol dependent individuals (Weissenborn & Duka, 2003; Fillmore et al., 2005; Goudriaan et al., 2007). MRI and fMRI studies have revealed alterations in brain structure (Pfefferbaum et al., 1997; Sullivan & Pfefferbaum, 2005; G. J. Harris et al., 2008) and brain activation differences during task performance (Braus et al., 2001; Tapert et al., 2001, 2004a; Grusser et al., 2004; Myrick et al., 2004; Heinz et al., 2007; Marinkovic et al., 2009; Trim et al., 2010; Paulus et al., 2012; Schuckit et al., 2012), which likely contribute to alcohol-related cognitive deficits. For a comprehensive review of studies investigating adult alcohol dependent populations using a wide variety of non-invasive (MR) and invasive neuroimaging techniques (requiring exposure to ionizing radiation in the form of X-rays or injection with radioactive isotopes, e.g. computed tomography, CT; positron emission tomography, PET; single photon emission tomography, SPECT), see (Buhler & Mann, 2011).

A growing body of literature has extended cognitive and neurobiological alterations observed in adult alcohol-using, abusing and dependent populations to now include alterations in brain structure and function, particularly in frontal networks and hippocampus, in adolescent and young adults with alcohol use disorders (AUDs) (De Bellis et al., 2000; Tapert et al., 2004b,c) and in adolescent binge drinkers (McQueeny et al., 2009; Schweinsburg et al., 2010). In an effort to address whether such alterations observed in adolescents with AUDs are antecedent to or consequences of alcohol use during this period of rapid brain development, studies have been conducted that examine adolescents who have not yet begun to drink or who have minimal alcohol use histories, but who are at risk for developing alcohol abuse problems, based on family history of alcoholism. Results from studies of youth that are family history positive for alcoholism (FH+) demonstrate significant differences in brain structure, function and cognition, as compared to youth with a negative family history (FH−). These findings suggest evidence for a unique genetic contribution that manifests prior to the initiation of alcohol use, and which may serve as a neurobiological vulnerability that confers higher risk for later alcohol abuse or dependence in FH+ youth (Poon et al., 2000; Hill, 2004; Schweinsburg et al., 2004; Silveri et al., 2004, 2008; Hill et al., 2007; Spadoni et al., 2008). An alternative, more rigorous approach is to use a prospective study design, in which adolescents who are alcohol naïve are enrolled at baseline and then followed over multiple, subsequent years. A significant proportion of adolescents initiate alcohol consumption at some point during the follow-up period, typically at rates that are consistent with epidemiological use data. In a study by Squeglia and colleagues (Squeglia et al., 2012), alcohol naïve adolescents at baseline who later transitioned into heavy drinking exhibited reduced fMRI responses (hypoactivation) during performance of a frontally-mediated working memory task at the initial visit, followed by hyperactivation in the same regions at follow-up. These findings suggest that patterns of brain activation observed prior to the onset of drinking may serve as a risk factor for future heavy alcohol use. In a second study, adolescents who had limited substance use at baseline but then transitioned to heavy alcohol use exhibited hypoactivation in frontal, parietal and

left cingulate regions during inhibitory processing compared with similarly-aged subjects who remained substance-use free (Norman et al., 2011). Taken together these valuable longitudinal results suggest that attenuated baseline brain activity, prior to the onset of alcohol use, may predict future substance use problems.

There have also been several proton MRS investigations conducted that have documented alterations in neurochemistry associated with alcohol abuse and alcoholism (Meyerhoff et al., 2013). However, it should be noted that the available MRS data have been limited to older alcohol dependent or recently abstinent alcoholic males (typically >40 years of age, except (Silveri et al., 2014), average age of 22 years) and only two reports to date have stratified drinking groups to investigate binge alcohol consumption (Meyerhoff et al., 2004; Silveri et al., 2014). Further, few studies have included a sufficient number of female participants to permit investigation of sex differences, and no published studies are available examining adolescent alcohol-using or abusing populations using MRS. Moreover, of the existing alcohol adult MRS studies, only six studies to date have examined *in vivo* brain GABA levels (Behar et al., 1999; Mason et al., 2006; Abe et al., 2013; Gomez et al., 2012; Mon et al., 2012; Silveri et al., 2014), although this is likely to change given increased accessibility to improved GABA detection and quantification methods (Mescher et al., 1998; Stagg et al., 2011b; Stagg, 2014). Recently, the first study employing MRS to measure *in vivo* GABA levels following an acute alcohol challenge was published (Gomez et al., 2012). In a cohort of healthy young adult social drinkers, occipital cortex (OCC) GABA levels decreased significantly (13 ± 8%) following intravenous alcohol infusion, which is consistent with alcohol's ability to potentiate the GABA system. A decrease in *in vivo* brain GABA levels in human brain following an IV alcohol challenge may seem counterintuitive given limited evidence that *in vivo* microdialysis studies in animals demonstrate increased GABA levels following an acute alcohol challenge, although findings are mixed. For instance, acute local ethanol increased GABA dialysate in central amygdala (Roberto et al., 2004), acute peripheral alcohol reduced GABA output in the nucleus accumbens (Piepponen et al., 2002) and ventral pallidum (Kemppainen et al., 2010), or had no effect in the nucleus accumbens (Heidbreder & De Witte, 1993), and acute oral alcohol dose had no effect in the ventral tegmental area–substantia nigra or ventral pallidum (Cowen et al., 1998). Alcohol effects on GABA levels in animal microdialysis studies are likely influenced by regionally specificity of alcohol effects on the GABAergic system, as well as by route of ethanol administration.

In vivo GABA levels measured using MRS reflect total GABA measured from the entire tissue within a voxel of interest, thus small extracellular increases in GABA that may be significant may not be detectable. Alternatively, Gomez and colleagues interpreted the reduction in GABA levels observed in healthy social drinkers during an IV alcohol challenge as reflecting acute reductions in GAD associated with alcohol infusion (Seilicovich et al., 1985). Indeed, other drug challenges that positively modulate the $GABA_A$ receptor are also associated with reductions in brain GABA levels measured using MRS, including reduced OCC GABA levels following an alprazolam challenge (Goddard et al., 2004) and reduced thalamic GABA levels following a challenge with zolpidem, a nonbenzodiazepine sedative/hypnotic positive modulator of the $GABA_A$ receptor (Licata et al., 2009). Given that the OCC GABA reduction observed in healthy social drinkers was maintained throughout the course of the 70 minute MRS acquisition, while subjects were clamped at a blood alcohol level of .06 mg/dL, it will be of interest in future studies to examine whether GABA changes associated with an alcohol challenge are similar in heavy drinking or dependent populations, are observed after oral exposure, or demonstrate unique time courses of recovery during the descending limb of the blood alcohol curve in dependent versus non-dependent cohorts. The remaining alcohol MRS studies have examined *in vivo* GABA levels in active heavy drinkers or recently abstinent alcohol dependent patients. Findings are detailed in Table 1 and are described below.

The first study, published in 1999 by Behar and colleagues (Behar et al., 1999), found that OCC GABA + homocarnosine was lower in five recently detoxified alcohol-dependent patients relative to healthy comparison subjects. Seven years later, Mason and colleagues (Mason et al., 2006) reported that GABA levels in the OCC did not differ significantly between previously alcohol-dependent patients and healthy subjects. In the Mason study, nonsmoking patients had higher GABA levels than smoking patients, however after one month of abstinence, GABA levels decreased significantly in nonsmokers but did not change in smokers. These first two GABA MRS studies document somewhat mixed findings in recently detoxified alcoholics. Although the investigations were limited to the OCC region, smoking status emerged as an important factor to consider when interpreting alcohol effects on brain GABA levels (Cosgrove et al., 2011). The next two studies, published more recently (2012 and 2013), examined brain GABA levels in regions other than the OCC: ACC, POC and DLPFC in alcohol-dependent individuals during early abstinence. The study by Mon and colleagues (Mon et al., 2012) found no differences in brain GABA levels at one month of abstinence in alcohol-dependent individuals compared to drug-free controls. In the study by Abe and colleagues (Abe et al., 2013), alcohol dependent poly-substance users demonstrated significant metabolic abnormalities in the DLPFC and a trend for lower GABA in the ACC, a pattern that was not observed in patients who were only alcohol dependent. While MRS GABA levels acquired in recently abstinent older adults appear largely normal relative to healthy comparison subjects

Table 1
MRS Studies of GABA and Alcohol.

	Subjects	Age	^{1}H MRS	Results
Silveri et al., 2014	23 BD (11f)	22	4 T SVS	⇓ ACC GABA: ⇓NP
	31 LD (13f)	22	ACC, POC	
Abe et al., 2013	40 AD (3f)	52	4 T SVS	no CON/AD differences ⇓ ACC Glu, NAA, Cr, GABA (trend only)
	28 AD + PSA (2f)	45	ACC, DLPFC, POC	
	16 CON (1f)	49		
Gomez et al., 2012	11 LD (8f) acute IV 6% ALC challenge (BrAC 60 mg/dl reached in 20 min)	26	4 T SVS OCC	⇓ GABA, NAA/NAAG 5 min post IV challenge
Mon et al., 2012	44 AD (5f) [20 baseline, 36 5 weeks ABST]	54	4 T SVS ACC, DLPFC, POC	⇓ ACC Glu, NAA, Cr, no GABA diff GABA normalized from 9 ± 4 to 34 ± 7 days of abstinence
	16 CON (2f)	49		
Mason et al., 2006	16 RDA (0f)	39	2.1 T SVS	Glu + Gln s > ns; ⇑NAA: ⇑ Glu + Gln ABST ⇓ GABA ns
	8 CON (0f)	39	OCC	
Behar et al., 1999	5 RDA (?f)	46	2.1 T SVS	⇓ GABA + homocarnosine: ⇓ NP
	10 CON (?f)	35	OCC	

Abbreviations: AD, alcohol dependent; ABST, abstinence; ALC, alcohol; BD, binge drinker; BrAC, breath alcohol concentration; CON, control; IV, intravenous; LD, light drinker; RDA, recently detoxified alcoholic; F, female; PSA, poly-substance abuse; (?) female n unspecified; SVS, single voxel spectroscopy; T, Tesla; ACC, anterior cingulate cortex; DLPFC, dorsolateral prefrontal cortex; OCC, occipital cortex; POC, parieto-occipital cortex; ⇑, significantly higher; ⇓ significantly lower; ns, not significant; :, related to; ns, non-smoker; s, smoker; >, greater than; Cr, creatine; GABA, gamma amino-butyric acid; Gln, glutamine; Glu, glutamate; NAA, N-acetyl-aspartate; NAAG, N-acetyl-aspartate glutamate; NP, neuropsychological performance.

in these two studies, GABA abnormalities in the ACC trended towards significance in concurrent alcohol and illicit drug users. In contrast, GABA MRS data from our laboratory, acquired from a significantly younger cohort of emerging adults (average age of 22 years), demonstrate significantly lower GABA levels in the ACC of binge versus light drinkers, while no differences were observed in a comparison region, the POC (Silveri et al., 2014). Taken together with ontogenetic changes in ACC GABA levels, it is plausible that the dynamically developing adolescent and late adolescent brain may be differentially sensitive to alcohol effects on brain GABA levels, which in turn could serve to modulate age differences in sensitivity to alcohol effects and to the development of alcohol tolerance. It is difficult to discern, however, whether or not low GABA levels observed in the ACC of emerging adult binge drinkers predate the initiation of alcohol consumption. Nevertheless, findings from studies conducted in recently abstinent, adult chronic alcohol abusers offer hope that metabolite abnormalities, GABA in particular, can recover with drinking cessation. Clearly more work is needed to tease apart the role of age of onset of alcohol use and the contribution of psychiatric co-morbidities, as well as to investigate potential relationships between GABA levels and cognitive functioning, all of which could help identify individuals most vulnerable to relapse.

Proton MRS methods for quantifying *in vivo* GABA metabolite levels using MRS have undergone significant advances over the past decade that have improved detection and quantification of this important neurotransmitter (Rothman et al., 1993; Keltner et al., 1997; Hetherington et al., 1998; Mescher et al., 1998; Jensen et al., 2005; Mekle et al., 2009; Puts & Edden, 2012). GABA levels measured using MRS likely reflect intracellular rather than intrasynaptic levels, since the majority of the GABA pool exists within GABAergic neurons (Petroff, 2002; Stagg et al., 2011b; Stagg, 2014), although determining such specificity is beyond the capabilities of current *in vivo* MRS (Stagg, 2014). To date, proton MRS remains the only non-invasive method capable of measuring *in vivo* brain GABA levels in humans, which is particularly advantageous for use in pediatric samples. That is, the non-invasive nature of MRS, compared to exposing the developing brain to radioactive isotopes required for other types of techniques for assessing *in vivo* GABA function (e.g., PET and SPECT), offers significant promise for future studies to track brain GABA changes associated with alcohol consumption and AUDs during adolescence.

Receptor imaging technologies that include PET and SPECT have been widely employed to probe the role of $GABA_A$ receptor function associated with alcohol dependence in adult populations (Cosgrove et al., 2011). For instance, $GABA_A$ receptor density can be inferred in PET using [^{11}C]flumazenil, and more recently [^{18}F]AH114726 (Rodnick et al., 2013), $GABA_A$ benzodiazepine receptor antagonists, and [^{123}I]iomazenil, a $GABA_A$ benzodiazepine receptor inverse agonist. Using these radiotracer methods, reduced $GABA_A$ receptor densities have been reported in 1-month, 3-month and 7-month abstinence alcohol dependent patients, and from brain regions that include the medial prefrontal cortex and cerebellum (Abi-Dargham et al., 1998; Lingford-Hughes et al., 1998, 2000, 2005). Conversely, elevated $GABA_A$ receptor density has been reported earlier during the course of abstinence, at 1-week, which normalized to control levels by 4-weeks (Staley et al., 2005). Taken together, these studies suggest that $GABA_A$ receptor density undergoes unique temporal changes during the course of recovery from alcohol dependence. Much like MRS, however, these invasive imaging techniques have their limitations, including exposure to radioactive isotopes and an inability to identify changes in $GABA_A$ receptor subunit composition or to differentiate between synaptic or extrasynaptic receptor subtypes. Despite advances in imaging technologies, there have yet to be published data from studies of alcohol dependent patients that combine MRS and PET to examine relationships between GABA concentrations and GABA receptor densities, respectively.

Within the framework of characterizing brain reorganization and rapid improvements in cognition during adolescence, this age span is already associated with a reduced capacity to evaluate and appropriately modulate response inhibition and emotional responses (Rubia et al., 2000; Luna & Sweeney, 2004; Yurgelun-Todd, 2007), related in part to the rapid maturation of frontal and limbic networks, and perhaps related to a developing GABAergic neurochemical system (Silveri et al., 2013). Accordingly, there are increased challenges within the context of healthy adolescent decision-making that are associated with immature neurobiological machinery, including making the decision to start drinking. That same decision of when to begin drinking not only influences the escalation of alcohol consumption and the likelihood of developing an alcohol use disorder later in life (Grant & Dawson, 1997; Hill et al., 2000; Brown & Tapert, 2004; Chassin et al., 2004), but also impacts healthy brain development. Due to ethical considerations against administering alcohol to human youth, to better understand the impact of use on multiple domains of development and functioning, animal studies have proven invaluable in identifying the consequences of alcohol use on the brain and on behavior in adolescents versus adults, under controlled laboratory conditions.

3. Preclinical evidence of adolescent-specific alcohol sensitivities

Over the past decade, there have been numerous reviews published, based on a multitude of empirical research articles, detailing a unique responsiveness of adolescents to alcohol effects (Chambers et al., 2003; Spear & Varlinskaya, 2005, 2010; Clark et al., 2008; Masten et al., 2008; Windle et al., 2008; Riggs & Greenberg, 2009; Schramm-Sapyta et al., 2009; Chin et al., 2010; Doremus-Fitzwater et al., 2010; Ehlers & Criado, 2010; Guerri & Pascual, 2010; Matthews, 2010; Witt, 2010; Spear, 2011b). These comprehensive reviews span basic and clinical studies and a variety of topics including neurodevelopment, neurocircuitry of motivation, impulsivity and addiction, age-specific alcohol sensitivities, reinforcing properties of alcohol (e.g., alcohol preference and self-administration), conditioned taste aversion to alcohol, development of tolerance, alcohol-induced withdrawal, and risk characteristics for alcohol initiation, escalation of use, and expression of alcohol use disorders. In summary, findings from an extensive collection of empirical preclinical studies illustrate both reduced (hyposensitivity) and enhanced (hypersensitivity) to alcohol effects in adolescents compared to adults.

In general, adolescents are less responsive (hyposensitive) than adults to sedation and motor impairment, and withdrawal-related anxiety, which typically serve to limit intake in humans. In contrast, greater responsiveness (hypersensitivity) to some of the cognitive impairing effects of alcohol has been reported, albeit data are somewhat mixed. While age-related differences in alcohol tolerance likely play a significant role in ontogenetic differences in alcohol sensitivity (Little et al., 1996; Silveri & Spear, 1998, 2001, 2004; Swartzwelder et al., 1998), adolescents are more sensitive to alcohol-induced reinforcement (Pautassi et al., 2008), with alcohol exposure during adolescence leading to an increased predisposition to later consume alcohol (Fabio et al., 2014). Thus, hypersensitivity to the positive rewarding effects of alcohol could serve to enhance intake. There is also a sizeable literature regarding ontogenetic differences in alcohol-related effects on social behavior, with adolescents demonstrating both greater and reduced sensitivity to unique dimensions of social facilitation and social inhibition, respectively (Varlinskaya et al., 1999, 2001; Varlinskaya & Spear, 2002, 2004b, 2006a,b, 2007). For the purposes of this review, discussion of adolescent-specific sensitivities to alcohol effects is limited to domains of sedation/ataxia, anxiety, and cognition.

3.1. Adolescent hyposensitivity to alcohol effects

Numerous studies have been published documenting that adolescents are significantly less sensitive than adults to the sedative/hypnotic and motor-impairing effects of alcohol. For instance, longer durations to lose the righting response (LORR) and quicker durations of time to regain the righting response (RORR) have widely been reported in response to acute or repeated alcohol challenges in adolescents relative

to adults (Little et al., 1996; Silveri & Spear, 1998, 1999, 2001, 2002; Swartzwelder et al., 1998). Chronic intermittent alcohol (CIE) exposure to high doses of alcohol have been shown to prevent the typical age-related increase in the alcohol-induced LORR, due in part to the development of alcohol tolerance (Silvers et al., 2003; Matthews et al., 2008). With regard to alcohol-induced motor incoordination, several studies demonstrate that adolescents are less impacted than adult counterparts when administered the same dose of alcohol based on body weight (Hollstedt et al., 1980; Little et al., 1996; White et al., 2002a,b; Ramirez & Spear, 2010). This age-related insensitivity is underscored by studies demonstrating that significantly higher doses of alcohol are necessary in adolescents to equate alcohol-induced impairments across ages (Silveri & Spear, 2001; Broadwater et al., 2011). Indeed, reduced responsiveness to alcohol-induced motor impairment is associated with high alcohol-seeking behavior, at doses that are reflective of those self-administered by adult alcohol-preferring rats (Bell et al., 2001), and in adolescent alcohol-preferring and high-alcohol-drinking rats (Rodd et al., 2004).

Anxiety-like behavior that accompanies alcohol withdrawal is typically significant but transient, lasting for longer durations following repeated intermittent bouts of intoxication (Zhang et al., 2007). To this end, a relative resistance to the anxiogenic behavioral effects of alcohol has also generally been observed following acute alcohol withdrawal in adolescents. While adults demonstrated anxiety-like behavior during acute alcohol withdrawal, measured using the elevated plus maze, similar anxiety profiles were not observed in adolescents, even when alcohol pharmacokinetics were considered (Doremus et al., 2003; Varlinskaya & Spear, 2004a). Similarly, acute alcohol withdrawal symptoms developed differentially in adolescent versus adult rats, depending on the anxiety symptoms being assessed (Slawecki & Roth, 2004; Slawecki et al., 2006). Anxiety-like behavior lasted up to one week following repeated alcohol withdrawals in adolescents, whereas anxiety-like behavior returned to baseline after 24 h in adults, suggesting that anxiety-like behavior associated with repeated withdrawals is more pronounced in adolescence than in adulthood (Wills et al., 2008, 2009). Finally, adolescent rats also demonstrate reduced sensitivity to seizure susceptibility during alcohol withdrawal (Acheson et al., 1999; Chung et al., 2008). In contrast, withdrawal severity did not differ between adolescents and adults when a modified Majchrowicz model of alcohol dependence was used to produce similar blood alcohol levels at an expected peak, despite administration of higher alcohol doses to adolescents (3 g/kg per day more) than adults, which was based on lower intoxication scores observed in the younger relative to the older group. Adolescents were qualitatively and quantitatively similar to adults in terms of withdrawal severity after the 4-day binge exposure period, suggesting that alcohol-related withdrawal behavior is largely dependent on blood alcohol levels, regardless of age (Morris et al., 2010). Taken together, adolescents are typically less sensitive to the physiological effects of alcohol, on measures of sedation, ataxia, acute withdrawal-related anxiety and seizure susceptibility, although there are some exceptions. Reduced sensitivity to these alcohol effects can therefore permit adolescents to consume greater amounts of alcohol on a given occasion compared to adults, perhaps given weak physiological feedback regarding intoxication that typically serves to reduce consumption or to terminate a drinking session.

3.2. Adolescent hypersensitivity to alcohol effects

In contrast to the observed physiological hyposensitivities, there is evidence that adolescents are hypersensitive to alcohol's effects on cognition. In work by Markeweise and colleagues (Markwiese et al., 1998), alcohol exposure was found to impair spatial memory acquisition in adolescent rats, but not in adult rats, and neither group showed impairment on a nonspatial memory task. Follow-up studies using the classic Morris Water Maze task demonstrate that alcohol-impairing effects on cognition are dose-dependent (Acheson et al., 2001), and that while alcohol-induced impairments are quickly reversed after treatment ends in adult animals, impairments in spatial memory persist well beyond the termination of repeated alcohol treatment in adolescents (Sircar & Sircar, 2005). Deficits in acquisition of spatial memory emerge in part due to slower learning associated with alcohol exposure in adolescents relative to adults (Novier et al., 2012). In work examining the effects of four weeks of CIE exposure during adolescence in rats, spatial working memory impairments persisted in young adults even after alcohol exposure had ended (Schulteis et al., 2008). Adolescent binge ethanol exposure was also reported to impair reversal learning on the Morris Water Maze and on the Barnes Maze when mice were when mice were assessed in adulthood (Crews et al., 2000; Coleman et al., 2011, 2014). Structural brain enlargements observed in adult orbitofrontal cortex, cerebellum, thalamus, internal capsule and genu of the corpus callosum were associated with adolescent binge ethanol exposure, and were hypothesized to lead to a lack of behavioral flexibility that may contribute to later impairments in spatial memory (Coleman et al., 2014). Using an appetitive conditioning paradigm, adolescents, but not adults, show impaired discrimination performance if training was followed by alcohol (Land & Spear, 2004a). In contrast, spatial acquisition in adolescents is not impaired on a less stressful sandbox maze relative to adults (Rajendran & Spear, 2004), or when alcohol exposure precedes learning to freeze to a tone (non-hippocampal dependent) or to a context (hippocampal dependent) (Land & Spear, 2004b).

Importantly, alcohol exposure, particularly CIE during adolescence, has been reported to produce cognitive tolerance to subsequent alcohol-induced spatial memory impairments that dissipates by adulthood (Silvers et al., 2003, 2006). However, studies addressing age-differences in metabolic alcohol tolerance highlight that blood alcohol levels alone do not solely underlie alcohol-induced spatial memory impairments (Van Skike et al., 2012), as the adolescent rat brain also demonstrates hypersensitivity to alcohol-induced brain damage when binge alcohol exposure occurs during adolescence compared to adulthood (Crews et al., 2000). Damage to anterior portions of the piriform and perirhinal cortices (important for memory), as well as frontal cortical olfactory regions, measured using an amino cupric silver stain procedure, was observed after four days of binge ethanol treatment in adolescent rats (P35) (Crews et al., 2000). As discussed in the subsequent section, GABAergic functional changes associated with adolescent alcohol exposure that lead to altered hippocampal physiology likely contribute to the ontogenetic profile of enhanced cognitive impairments associated with alcohol exposure during adolescence (Slawecki et al., 2001; Tokunaga et al., 2006).

3.3. Role of γ-amino-butyric acid (GABA) in adolescent alcohol responsiveness

It is plausible that the differential sensitivities to alcohol action in adolescents contribute to an increased tendency for greater alcohol consumption, subsequently leading to neurobiological adaptation to chronic alcohol exposure. Indeed, unique adolescent maturational profiles of central target sites of alcohol action, e.g., GABA and glutamate (Deitrich et al., 1989; R. A. Harris et al., 2008; Kumar et al., 2009), may contribute to the neurobiological underpinnings of some of the adolescent-specific sensitivities observed to alcohol effects.

Importantly, $GABA_A$ agonists and NMDA antagonists have been shown to potentiate the hypnotic effects of alcohol in adult rats (Liljequist & Engel, 1982; Beleslin et al., 1997). To the extent that ontogenetic differences in neural mechanisms might underlie the relative resistance of young animals to alcohol, psychopharmacological manipulations targeting GABA and NMDA receptor systems were found to differentially modulate age differences in alcohol responsiveness in adolescent and adult rats (Silveri & Spear, 2002, 2004). As can be seen in Fig. 3, the NMDA antagonist, (+)MK-801, administered prior to a sedative dose of alcohol, significantly increased alcohol-induced sedation at both ages, but maintained the age-related increase

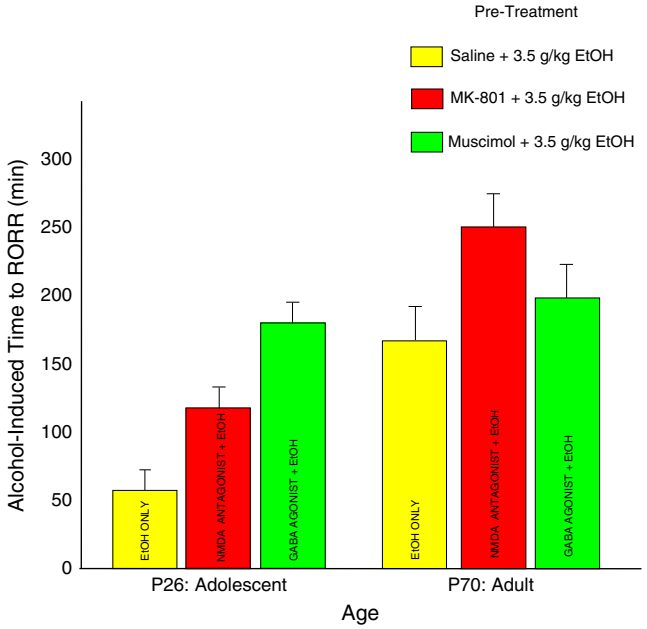

Fig. 3. Each bar represents data from n = 12 (collapsed over sex) Sprague–Dawley rodents intraperitoneally (ip) injected on postnatal (P) day 26 (adolescents, left set of three bars) or P70 (adults, right set of three bars) with 0.9% saline vehicle (yellow bars), 0.10 mg/kg of the NMDA antagonist (+)-5-methyl-10,11-dihyrdro-5H-dibenzo[a,d]-cyclo-hepten-5,10-imine hydrogen maleate [(+)MK-801] (red bars), or 1.25 mg/kg of the GABA agonist muscimol (green bars). Ten minutes after pretreatment administrations, all animals received an ip injection of 3.5 g/kg of ethanol (ETOH, 17% v/v; diluted with 0.9% saline). Alcohol-induced sedation was measured as the time to RORR (min) as a function of pretreatment [saline, (+)MK-801, or muscimol] and age. Data are expressed as means ± SEM. See also Silveri and Spear (2002, 2004).

in sensitivity typically observed. In contrast, adolescents were considerably more sensitive to pretreatment with the $GABA_A$ agonist muscimol, which enhanced alcohol sedation to a greater degree in adolescents than in adults. Although modulation of both systems enhanced sedative effects of alcohol across ages, stimulation of the $GABA_A$ receptor was a more effective means of enhancing alcohol sedation in adolescents (Fig. 3). Given that ontogenetic changes in sensitivity to alcohol sedation are related to a notable age decline in acute tolerance, acute tolerance observed in adolescents was found to be disrupted by (+)MK-801 but not muscimol (Silveri & Spear, 2004). It is plausible that the observed differences are related to differences in the mechanism by which muscimol and +MK-801 target their receptors. Nonetheless, pharmacological attenuation of the expression of acute tolerance was sufficient but not necessary to delay RORR after alcohol. These data suggest that maturation of the GABA and glutamate systems may uniquely contribute to a notably reduced sensitivity to alcohol sedation during ontogeny. Indeed, not only does repeated alcohol exposure lead to the development of alcohol tolerance, both metabolic and neuronal, the latter of which is likely associated with $GABA_A$ receptor down regulation, a combination of reduced GABA concentrations associated with ontogenetic state and alcohol-related changes in expression and responsiveness of GABA receptors could have significant ramifications for the observed behavioral sensitivity to alcohol. For a review of GABA-related alcohol tolerance mechanisms associated with acute and chronic exposure, see work by Kumar and colleagues (Kumar et al., 2009).

Adolescents were also reported to be less sensitive to a zolpidem, a positive allosteric modulator of the $GABA_A$ receptor, compared to older counterparts (Moy et al., 1998). Measurement of [^{3}H]zolpidem binding in that same study revealed age-related increases in binding, with binding in the cingulate cortex, medial septal nucleus, globus pallidus, inferior colliculus, red nucleus, and cerebellum, increasing up to day P20, stabilizing from P20 through P28, and followed by a subsequent increase into adulthood. Thus, consistent with $GABA_A$ and NMDA manipulation studies, adolescent-hyposensitivity to alcohol sedation appears to be coincident with developmental changes in $GABA_A$ receptor sites targeted by [^{3}H]zolpidem (Moy et al., 1998). To the extent that GABA also plays a role in alcohol-induced seizure susceptibility (Olsen & Spigelman, 2012), when pentylenetetrazole was used to induce seizures during alcohol withdrawal, seizures were significantly shorter in adolescents compared to adults (Acheson et al., 1999). In contrast, modulation of the $GABA_A$ receptor with acute alcohol or the neuroactive steroid allopregnanolone did not differentially impair the retrieval of spatial memory on the Morris water maze between adolescents and adults (Chin et al., 2011).

Recent mounting data from molecular, cellular and behavioral studies implicate perhaps a more notable role of $GABA_A$ type receptors in the adaptations to alcohol, including voluntary intake, dependence and withdrawal (Grobin et al., 1998). For instance, the $GABA_A$ agonist THIP increased intake of and preference for alcohol, while the GABA antagonist picrotoxin decreased intake of and preference for alcohol, over baseline levels in adult rodents (Boyle et al., 1993). In adolescents, however, lorazepam, also a $GABA_A$ positive modulator, increased 60-minute food intake, whereas the neuroactive steroid DHEA decreased food intake on injection days. In adulthood, lorazepam-treated animals preferred the lowest concentrations of alcohol + saccharin more than saccharin alone, compared with vehicle-treated subjects who showed no preference for any concentration of alcohol + saccharin over saccharin. DHEA-treated animals, however, showed no preference for any of the available solutions. These data demonstrate that $GABA_A$ receptor modulation during adolescence can alter intake and preference for ethanol in adulthood, highlighting the importance of drug history as an important variable in the liability for alcohol abuse (Hulin et al., 2012). In contrast, it was reported that exposure to alcohol during adolescence does not necessarily enhance ethanol's reinforcing properties later in life, findings that could have been related to ethanol initiation/oral self-administration procedures (Tolliver & Samson, 1991). In general, these studies suggest evidence for a diminished potency of alcohol as a positive $GABA_A$ modulator, which likely contributes to the reduced sensitivity of adolescents to alcohol effects. Therefore, while alcohol interacts with multiple neurotransmitters systems and receptors, including NMDA, it seems GABA may be one of the most influential in terms of mediating alcohol effects during adolescence.

Although there are mixed results regarding the behavioral effects of alcohol on cognition in adolescent rats, there is a consistent line of evidence documenting enhanced sensitivity to alcohol effects on hippocampal physiology. Hippocampal long-term potentiation (LTP), one of the major cellular mechanisms underlying learning and memory, is attenuated by alcohol exposure. To this end, there are studies documenting hypersensitivity of adolescent hippocampal tissue slices to the inhibitory potency of NMDA receptor-mediated synaptic activity to alcohol (Swartzwelder et al., 1995; Pyapali et al., 1999). Since publication of these seminal ontogenetic alcohol-LTP studies, attention has shifted to examining differential ontogenetic contributions of GABA to alcohol effects on hippocampal physiology. Adolescent hypersensitivity reported for alcohol effects on hippocampal physiology include greater alcohol-induced GABA-mediated inhibitory postsynaptic potentials (IPSPs) in hippocampal CA1 pyramidal cells (Li et al., 2003, 2006) and enhanced extrasynaptic $GABA_A$ receptor mediated tonic currents in dentate granule cells (Fleming et al., 2007). Increases in spontaneous firing characteristics and hyperpolarization-activated cation current of hippocampal interneurons were also significantly more pronounced in adolescents than adults, and also persisted in the presence of glutamatergic and GABAergic blockers (Yan et al., 2009). In contrast, evoked $GABA_A$ receptor-mediated inhibitory postsynaptic currents (IPSCs) were less powerfully enhanced by acute alcohol in adolescents than in adults (Li et al., 2006). Furthermore, when adolescents received CIE, long-lasting changes in the sensitivity of extrasynaptic $GABA_A$ receptors to alcohol were observed in dentate gyrus cells in adulthood. Thus,

$GABA_A$ receptor changes may "lock-in" adolescent hypersensitivity to alcohol in these cells that extend into adulthood (Fleming et al., 2012). Overall, greater alcohol alterations in hippocampal physiology after alcohol exposure are consistent with a heightened sensitivity to alcohol-induced memory impairments in adolescents (Li et al., 2002). Thus, these studies point to the conclusion that developmental differences in the effects of alcohol on interneuron excitation, which likely contributes to age-differences in alcohol effects on cognition, reflect enhanced sensitivity of $GABA_A$ receptor-mediated IPSCs in adolescents compared to adults.

While it has been well established that alcohol enhances the function of $GABA_A$ receptors (for a comprehensive reviews see Ueno et al., 2001; Kumar et al., 2009), studies are beginning to elucidate the roles of specific receptor subtypes in alcohol-induced behaviors (Boehm et al., 2004, 2006; Wallner et al., 2006; Korpi et al., 2007; R. A. Harris et al., 2008; Lobo & Harris, 2008). For instance, evidence from GABA receptor subunit knockout studies demonstrate that some alcohol-related behaviors are dependent on α_2-containing $GABA_A$ receptors, such as the development of a conditioned taste aversion to alcohol (Blednov et al., 2013) and alcohol-induced motor stimulant effects (Blednov et al., 2011), albeit there is some conflicting evidence (Lovinger & Homanics, 2007). It is tempting to categorize subunit involvement by behavioral alterations demonstrated by receptor subunit knock-in and knock-out studies, e.g., altering α_1 subunit composition alters sedation, $\alpha_{2/3}$ alters anxiety and $\alpha5$ alters temporal and spatial memory, however "behavior is a complex phenomenon, and most probably, there are several types of $GABA_A$ receptors involved in even simple behavioral traits" (Sigel & Steinmann, 2012). Nonetheless, enhanced GABAergic function, as it relates to high alcohol preference (Hwang et al., 1997), warrants investigation of the potential interplay between ontogenetic changes in GABA subunits and the unique profile of behavioral sensitivity to alcohol effects observed during adolescence.

Finally, aside from alcohol's ability to act as a $GABA_A$ receptor positive modulator, alcohol also increases levels of some neuroactive steroids, including 3α,5α-THP and 3α,5α-THDOC, which have been reported to enhance GABAergic neurotransmission, potentially influencing the behavioral effects of alcohol (Kumar et al., 2009). Acute alcohol intoxication has also been shown to increase levels of the neuroactive steroid allopregnanolone in the hippocampus of rodents tested during adulthood (P52 and P60), however the alcohol-related increase in allopregnanolone levels was blunted by CIE during adolescence (Silvers et al., 2006). Likewise, elevated allopregnanolone levels have been reported in human adolescents in association with acute alcohol intoxication (Torres & Ortega, 2003, 2004). Of note, consistent with previous adult GABA MRS data (Epperson et al., 2002, 2005, 2006), there is evidence for an influence of menstrual cycle phase, when circulating sex hormones vary, on brain GABA levels measured in both adolescents and emerging adults. Luteal phase (peak estrogen at ovulation followed by declining levels, and high levels of the neuroactive steroid, progesterone) females exhibit lower GABA levels relative to females tested during the follicular phase (low estrogen, low progesterone) (Silveri et al., 2013). Given the ongoing hormonal changes that accompany brain development and adolescence in general (Blakemore et al., 2010), studies are needed to investigate potential hormone–GABA interactions that could influence alcohol effects during this critical age period. It is plausible that alcohol sensitivity is not only modulated by $GABA_A$ receptor activity (Morrow et al., 2001), but that adolescent-specific sensitivities associated with an immature GABA system may be driven in part by age differences in levels of circulating neurosteroids, the ability of alcohol to modulate neurosteroid levels, and/or alcohol-neurosteroid interactions at the $GABA_A$ receptor.

4. Translating to the human condition: *in vivo* γ-amino-butyric acid (GABA) MRS studies

As discussed in previous sections, *in vivo* frontal lobe GABA levels, measured using MRS, were lower in healthy adolescents than in healthy emerging adults, yet GABA levels were lower, higher or unaffected in MRS studies of older adults that were recently abstinent from alcohol use. While it would be extremely valuable to conduct an MRS investigation of brain GABA levels in adolescents with alcohol use disorders, it is notable that low *in vivo* GABA levels have been implicated in a number of other psychopathological conditions in adults, including depression, anxiety, epilepsy, cocaine and alcohol dependence (Chang et al., 2003). Moreover, *in vivo* GABA levels observed in adult human MRS studies significantly predict motor control, anxiety symptoms and cognitive performance, akin to measures that demonstrate differential alcohol effects in ontogenetic animal studies.

Advances in the reliability and versatility of MRS methods available for measuring GABA via MRS provide a valuable step forward (Mullins et al., 2014), particularly given the high spatial resolution afforded by combining MRI with MRS in order to acquire and quantify GABA levels across multiple brain regions. While it will be important in future studies to examine relationships between brain GABA levels and GABA receptor density in alcohol dependence and following chronic treatments for alcoholism that involve modulation of the GABA system, the following studies offer important insights for understanding the role of *in vivo* brain concentrations of GABA in various healthy behaviors, as well as in a number of clinical conditions.

4.1. Motor control and sleep

It has been reported that alcohol consumption impairs motor ability at blood alcohol levels at 0.06% and higher, including but not limited to alterations in postural control (Modig et al., 2012), delayed compensatory muscle responses (Woollacott, 1983), and impaired driving ability (Ferrara et al., 1994; Martin et al., 2013). A number of MRS studies have been published that confirm an important role of GABA levels in motor control, although none have investigated GABA levels associated with the effects of an acute alcohol challenge on motor control. Nonetheless, developmental increases in GABA from adolescence to emerging adulthood were associated with lower motor impulsivity (Silveri et al., 2013). In healthy adults, trait urgency in healthy men correlated with DLPFC GABA levels, with higher GABA predicting lower urgency scores (Boy et al., 2011), and better responsiveness of subconscious motor mechanisms was related to higher GABA levels in the supplementary motor area (Boy et al., 2010). Higher GABA levels were also associated with slower reaction times (Stagg et al., 2011a) and predicted a better ability to rapidly resolve shifting gaze from one stimulus over another (Sumner et al., 2010). Finally, higher frontal lobe GABA levels were correlated with lower extroversion personality traits in healthy individuals (Goto et al., 2010). Across each of these adult studies, higher GABA levels were associated with better motor control. On the contrary, low GABA levels, as is the adolescent phenotype, is associated with worse motor control or with heightened impulsivity. To translate these GABA findings into interpretation for adolescent-specific alcohol sensitivities, adolescents are less sensitive to the motor incoordinating effects of alcohol, presumably due to a diminished potency of alcohol as a positive GABA modulator to produce motor incoordination at this age, unless significantly higher blood alcohol levels are achieved (relative to adults).

In addition to motor-impairing effects, acute alcohol has a soporific effect, which manifests as sedation. While rodent studies assessing alcohol-induced sedation largely reflect loss of a reflexive response rather than sleep per se, disturbed sleep produced by chronic alcohol abuse in humans is predictive of relapse drinking after periods of abstinence (Brower et al., 1998; Gann et al., 2001; Brower, 2003). Chronic alcohol treatment produces similar sleep-related deficits in rats, including REM suppression, difficulty falling asleep, and difficulty remaining asleep (Mukherjee & Simasko, 2009). Alcohol-preferring rats were also more susceptible to sleep disruptions after binge alcohol exposure, as evidenced by a significant reduction in nonREM sleep and increased wakefulness the day after treatment (Thakkar et al., 2010). Although no MRS

studies to date have investigated sleep disturbances in relation to brain GABA levels in alcohol dependent patients, altered GABA levels have been reported in patients with sleep disorders. Brain GABA levels, acquired from a large brain region including basal ganglia, thalamus, and temporal, parietal, and occipital white matter and cortex, were ~30% lower in patients diagnosed with primary insomnia relative to individuals without sleep complaints (Winkelman et al., 2008). Furthermore, low GABA levels were negatively correlated with a faster wake after sleep onset on polysomnography measures (Winkelman et al., 2008). In a subsequent regional investigation, low GABA levels were regionally specific to the ACC and POC, but not the thalamus of patients with primary insomnia (Plante et al., 2012a). When MRS data were acquired in the evening, however, OCC GABA levels were elevated in primary insomnia patients relative to the comparison group (Morgan et al., 2012; Plante et al., 2012b). Although diurnal stability of OCC GABA levels has been documented in healthy adults (Evans et al., 2010), there is evidence of significantly lower frontal lobe GABA levels in an alternate-shift group compared to a day-shift group, highlighting the impact of an irregular work schedule on the maintenance of GABA levels (Kakeda et al., 2011). Not surprisingly, sleeps aids such as a zolpidem, which modulates the $GABA_A$ receptor, decreased GABA levels in the thalamus, but not in the ACC, likely reflecting GABA turnover in healthy adult volunteers (Licata et al., 2009). Furthermore, administration of propofol, a hypnotic agent used to induce and maintain general anesthesia, significantly increased GABA levels in motor cortex, sensory cortex, hippocampus, thalamus and basal ganglia in healthy young adult volunteers in an unconscious state (Zhang et al., 2009). Indeed, the unique developmental changes in the sedative effects of alcohol, coupled with changing sleep mechanics during adolescence (Colrain & Baker, 2011) and the impact of alcohol use on sleep quality (Ehlers & Criado, 2010), data from MRS GABA studies of sleep disorders and sedative/hypnotic agents provide interesting potential new directions for adolescent brain research investigating the impact of alcohol use on sleep physiology.

4.2. Anxiety and seizure disorders

Anxiety and seizure are associated with alcohol withdrawal, and are present typically in early abstinence. To draw connections to the GABA system, a growing number of MRS investigations have identified that GABA levels are low in patients with anxiety disorders, including individuals with panic disorder, social phobia and obsessive–compulsive disorder (OCD). Patients with panic disorder exhibit lower OCC GABA levels (Goddard et al., 2001) and an impaired GABA response to an acute benzodiazepine challenge (Goddard et al., 2004). Low GABA was also reported in the ACC and basal ganglia of medicated subjects with panic disorder (Ham et al., 2007), although levels were not different in other PFC areas (Hasler et al., 2009). More recently, evidence of low GABA in the ACC and medial PFC, was reported in a third study of patients with panic disorder. Notably, in that study, GABA differences were more pronounced in individuals with a family history of panic disorder (Long et al., 2013). Less data are available from patients with other types of anxiety disorders, although thalamic GABA was lower in patients with social anxiety disorder (Pollack et al., 2008) and medial PFC GABA was lower in patients with OCD (Simpson et al., 2012). Interestingly, yoga practice, a lifestyle variable, was found to not only enhance GABA levels in healthy adults, but increased GABA was significantly correlated with lower anxiety and depression scores after completing a 12-week yoga regimen (Streeter et al., 2007, 2010). These benefits of yoga are hypothesized to result from increased activity in the parasympathetic nervous system and enhanced GABAergic activity, which could help to ameliorate symptoms across a variety of diseases (Streeter et al., 2012). Finally, ACC GABA levels were positively associated with harm avoidance temperament in healthy subjects, suggesting a potential link between neurochemistry and responsiveness to fear and anxiety (Kim et al., 2009). Thus, manifestation of abstinence-related anxiety symptoms may be associated with an alcohol-related reduction in GABA levels in adults, whereas in adolescents, alcohol less potently modulates already low GABA levels, thereby minimizing the manifestation of anxiety symptomatology. To the extent that anxiety disorders are often present in adolescents, regardless of alcohol use, future investigations of GABA levels in human adolescents should directly assess relationships with anxiety profiles.

Alcohol abstinence is also associated with increased seizure vulnerability. There is a compelling literature implicating low GABA in epilepsy and documenting successful pharmacological interventions for seizure disorders that are effective via the modulation of GABA (Petroff et al., 1996a,b, 1999; Mueller et al., 2001; Doelken et al., 2010; except Simister et al., 2003, 2009). Low brain GABA levels were associated with poor seizure control in patients with complex partial seizures (Petroff et al., 1996b). Furthermore, low GABA levels in the primary somatosensory cortex of patients with chronic epilepsy were significantly correlated with elevated levels of antibodies to GAD, reflecting GABA synthesis (Stagg et al., 2010). Brain GABA levels, measured using MRS in the OCC, increased significantly following treatment with the antiepileptic drug vigabatrin, which irreversibly inhibits GABA-T. The response of brain GABA levels to vigabatrin not only predicted improved seizure control in epileptic adults (Petroff et al., 1996a), but also permitted the identification of positive responders (those with reduced seizure activity) to vigabatrin based on lower baseline GABA levels and a more pronounced GABA increase during treatment (Mueller et al., 2001). MRS measurements of brain GABA have also been used successfully to monitor treatment responses to vigabatrin in children with epilepsy (Novotny et al., 1999).

Two studies combining MRS, to measure brain GABA levels, and SPECT or PET, to measure $GABA_A$ benzodiazepine receptor binding, have also been published. In adult patients with partial seizures, OCC GABA levels increased three fold after 25–84 days after treatment with vigabatrin, although benzodiazepine binding (measured using [^{123}I]iomazenil] SPECT) did not change (Verhoeff et al., 1999). Similarly, three days of treatment with vigabatrin increased OCC GABA levels in healthy adult volunteers, however no evidence of $GABA_A$ receptor down regulation (measured using ^{11}C-flumazenil (FMZ)-PET) in response to elevated GABA levels was observed (Weber et al., 1999). Other antiepileptic drugs targeting the GABAergic system used for managing seizures have also been shown to elevate GABA levels measured using MRS, in human and rodent tissue. There was a 62% increase in GABA concentration following vigabatrin applied to human neocortical tissue resected during epilepsy surgery, as well as a 13% increase in GABA concentrations following application of gabapentin, an analogue of GABA. Although there was an 82% increase in GABA following vigabatrin applied to healthy tissue from rodents, there were minimal effects of gabapentin on GABA concentrations (non-significant 2% increase in GABA) (Errante et al., 2002). Finally, topiramate, a broad spectrum antiepileptic drug that enhances $GABA_A$ receptor mediated Cl^- flux, among other actions, likewise increased brain GABA in the OCC of epileptic patients, offering partial protection against further seizure activity (Petroff et al., 2001).

Given that low GABA levels may convey vulnerability to developing AUDs in adolescents and adults, drugs utilized to increase GABA levels in seizures disorders could be used to test such a hypothesis. To this end, although there have been no published MRS studies examining the effects of GABA promoting agents on GABA levels in alcohol dependent patients, there is growing interest in the use of medications acting on the GABA system for treating alcohol dependence (Caputo & Bernardi, 2010), use of new non-benzodiazepine GABAergic medications for treating alcohol-related withdrawal syndrome (Leggio et al., 2008), and in the role of $GABA_B$ receptors in addiction in general (Tyacke et al., 2010).

4.3. Cognition

As previously outlined, alcohol exposure (acute and chronic) impairs cognitive functioning across multiple domains (Oscar-Berman,

1990, 2000; Parsons & Nixon, 1998; Oscar-Berman & Marinkovic, 2003). Most of the available studies reporting relationships between MRS-derived measures of GABA and cognitive performance are based on data acquired from healthy populations, although there are some reports of GABA-cognition correlations in alcohol abusing populations and in patients with schizophrenia. It is unequivocally accepted that cognition abilities rapidly improve during childhood and adolescence, but then slowly deteriorates into senescence. Interestingly, based on the limited data available, *in vivo* brain GABA levels follow a similar inverted U-shaped curve and cognition, increasing during adolescence (Silveri et al., 2013) and decreasing into older adulthood (Gao et al., 2013). Notably, developmental changes in GABA are observed in brain regions (e.g., frontal lobe) that mediate higher order cognitive abilities, such as executive functioning. This domain of cognitive functioning is also particularly vulnerable to chronic alcohol use (Oscar-Berman, 2000; Sullivan & Pfefferbaum, 2005).

The limited number of studies addressing relationships between *in vivo* brain GABA levels and cognition is related to the recent evolution in the technology required for acquiring GABA metabolite data, i.e., refinement of GABA-optimized MRS sequences, and availability of state-of-the-art head coils and MR scanners. One of the earliest reports documenting a relationship between GABA and cognition found that higher GABA in the primary visual cortex was associated with better performance on a visual discrimination task (Edden et al., 2009). Healthy subjects who showed greater tactile frequency discrimination also had higher GABA levels in the sensorimotor cortex (Puts et al., 2011). Although cognition was not tested per se, higher ACC resting state GABA concentrations strongly predicted negative fMRI responses while making emotional judgments (Northoff et al., 2007). Since negative fMRI responses are coupled to decreased neuronal activity, i.e., neuronal inhibition (Shmuel et al., 2002, 2006; Pasley et al., 2007), these findings provide important evidence linking brain GABA levels with functional brain activation responses during emotional processing. In adolescents, significant correlations were observed between higher ACC GABA levels and better percent accuracy on No-Go inhibition trials (Silveri et al., 2013). In contrast, ACC GABA did not significantly predict performance on an alternative response inhibition task, the Stroop Color-Naming task (Silveri et al., 2013). Thus, GABAergic contributions may not necessarily generalize across impulse control indices, particularly when cognitive control tasks require differing sensory or response demands (Stevens et al., 2007). Levels of GABA in the POC were not predictive of response inhibition ability, and ACC GABA did not significantly relate to other aspects of cognition, e.g., attention, memory, or general intelligence, suggesting that GABA and cognition relationships have unique regional significance. In contrast, greater decreases in GABA levels in the primary motor cortex following transcranial direct current stimulation (tDCS) were associated with better short-term motor learning, supporting the notion that LTP-dependent learning is dependent on GABA modulation (Stagg et al., 2011a). In addition, a balance of low GABAergic inhibition and high glutamatergic excitation in the ventromedial PFC of human volunteers predicted better behavioral performance on a reward-guided decision-making task (Jocham et al., 2012).

In a cohort of alcohol-dependent patients who had lower OCC GABA + homocarnosine than healthy comparison subjects, low GABA was significantly associated with worse delayed verbal memory performance (Behar et al., 1999). GABA levels in ACC, POC or DLPFC, however, did not predict neurocognitive performance in separate cohorts of recently detoxified alcoholic patients (Abe et al., 2013; Mon et al., 2012), however, ACC GABA was negatively correlated with auditory verbal learning and POC GABA was positively correlated with visuospatial memory, but only in former alcoholic patients who were also poly-substance users (Abe et al., 2013). In our study of emerging adults (ages 18–24 years), significantly lower ACC GABA levels predicted worse response inhibition on No Go trials and worse attention/mental flexibility on the Trail Making Test in binge drinkers, a pattern that was not observed for POC GABA levels, or in either region in light drinkers (Silveri et al., 2014). Finally, in a cohort of patients with schizophrenia, lower GABA in the visual cortex was significantly correlated with worse orientation-specific surround suppression, a behavioral measure of visual inhibition requiring contrast discrimination (Yoon et al., 2010). On the other hand, unmedicated patients with schizophrenia had elevated medial PFC GABA levels relative to medicated patients and comparison subjects, although there were no significant correlations observed between DLPFC or medial PFC GABA levels and working memory performance (Kegeles et al., 2012).

Findings from MRS studies examining relationships between GABA levels and cognitive performance are more varied than relationships between GABA, motor measures and anxiety symptoms. In general in healthy individuals, higher GABA levels predict better performance for discrimination or response inhibition tasks, whereas lower GABA levels predict better performance on memory tasks. In patient populations, there are mixed findings of lower GABA and worse memory, inhibition and abstract reasoning, as well as a lack of significant relationships between GABA levels and cognitive performance. Future studies investigating relationships between GABA levels and cognitive impairments associated with active alcohol use are clearly warranted. Furthermore, learning and memory and decision-making are cognitive processes that are crucial elements for the successful navigation through adolescence. Given the vulnerabilities of these processes to alcohol use and the ongoing developmental changes in the GABA system, initiation and escalation of alcohol use during this time could perpetuate an already heightened level of risk-taking, as well as alter the healthy maturation of this very important neural system that could lead to increased risk for developing alcohol use disorders.

5. Summary

Over the past two decades, there has been a dramatic increase in knowledge regarding adolescence, through characterization of neurodevelopmental changes captured non-invasively in humans using a variety of MR techniques and from animal studies that have demonstrated adolescence to be a period of unique sensitivity to alcohol effects. Taken together, there are increasing opportunities for translation between findings from animal and human models, in order to gain the most comprehensive understanding of the consequences of alcohol use on the adolescent brain. As discussed in this review, low *in vivo* brain GABA levels have been reported in healthy adolescents, alcohol use disorders, and psychiatric disorders. To this end, *in vivo* brain GABA studies using MRS offer new possibilities for probing the GABAergic system in both basic and clinical studies, which could provide valuable information that could lead to the development of new interventions for treating alcohol use disorders.

Neuroimaging methods capable of capturing dynamic changes in GABAergic function provide an important step forward, particularly in light of $GABA_A$ receptor subunit studies that have identified genetic markers associated with increased risk for alcohol dependence. For instance, studies examining variations in single-nucleotide polymorphisms (SNPs) in GABA receptor genes have revealed associations between genetic variations in GABRA1, GABRA2, and GABRG3 and alcohol dependence and behavioral endophenotypes associated with risk for alcoholism, some of which vary by the chromosome investigated. Chromosome 5q GABA receptor gene variations were found to not play a strong role in alcohol dependence (Dick et al., 2005), but a subsequent study reported that variations in GABRA1 on chromosome 5q were associated with a less severe phenotype of alcohol dependence, history of alcohol-induced blackouts, age of first drunkenness and subjective responsiveness to alcohol (Dick et al., 2006b). There is ample evidence that GABRA2 variations are also associated with alcohol and other substance use disorders (Covault et al., 2004; Edenberg et al., 2004; Lappalainen et al., 2005; Fehr et al., 2006; Enoch, 2008; Soyka et al., 2008) except (Matthews et al., 2007). More recently, variations within GABRA2 were associated with an attenuated negative response

to an oral alcohol challenge, which reflects a reduced sensitivity to the effects of alcohol that is a risk factor vulnerability to developing alcohol use disorders (Uhart et al., 2013). In a study examining multiple developmental stages, GABRA2 variations were associated with childhood conduct disorder symptoms but not childhood alcohol dependence symptoms. Importantly, evidence for a consistent elevation in risk for alcohol dependence associated with GABRA2 did not manifest until the mid-20s, lasting into adulthood (Dick et al., 2006a). More recently, adolescent GABRA2 was strongly associated with sensation-seeking behavior, a hallmark of this age period, and the potential pathway by which GABRA2 confers risk for developing alcohol use disorders via an early drive to experiment with alcohol (Dick et al., 2013). GABRG3 variations on chromosome 15q have also been shown to be associated with risk for alcohol dependence (Dick et al., 2004), as well as variations in genes coding for other neurotransmitters, such as glutamate and serotonin (Hu et al., 2005; Edenberg & Foroud, 2006; Schumann et al., 2008). Nonetheless, combination of *in vivo* GABA MRS studies in combination with genetic assessments of variations in GABA-specific genes will provide a powerful future perspective across multiple levels of analysis.

Finally, pharmacological treatments targeting the GABA system have been efficacious for treating multiple psychiatric conditions (Krystal et al., 2002; Sanacora et al., 2002, 2003; Bhagwagar et al., 2004; Streeter et al., 2005). Therapies such as cognitive behavioral therapy have a more modest effect on brain GABA levels compared to other pharmacological interventions; however, significant associations between the degree of post-treatment GABA increases and decreases in psychiatric symptoms (Sanacora et al., 2006) offer promise for similar studies that monitor GABA levels using MRS to identify responsiveness to treatment interventions for alcoholism. Indeed, neurochemical alterations associated with adolescent alcohol abuse and other disorders could inform the development of novel treatment strategies that target GABA, which could enhance functioning and boost mood, and perhaps reduce drinking, via modulation of the GABAergic system. In conclusion, *in vivo* brain GABA MRS offers a new lens through which the neurophysiology of adolescent-specific sensitivities to alcohol can be viewed, particularly in light of significant developmental changes in the GABAergic system.

Conflict of interest

The author declares that there are no conflicts of interest.

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