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Review article

The role of MRS-assessed GABA in human behavioral performance

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ABSTRACT

Understanding the neurophysiological mechanisms that drive human behavior has been a long-standing focus of cognitive neuroscience. One well-known neuro-metabolite involved in the creation of optimal behavioral repertoires is GABA, the main inhibitory neurochemical in the human brain. Converging evidence from both animal and human studies indicates that individual variations in GABAergic function are associated with behavioral performance. In humans, one increasingly used in vivo approach to measuring GABA levels is through Magnetic Resonance Spectroscopy (MRS). However, the implications of MRS measures of GABA for behavior remain poorly understood. In this respect, it is yet to be determined how GABA levels within distinct task-related brain regions of interest account for differences in behavioral performance.

This review summarizes findings from cross-sectional studies that determined baseline MRS-assessed GABA levels and examined their associations with performance on various behaviors representing the perceptual, motor and cognitive domains, with a particular focus on healthy participants across the lifespan. Overall, the results indicate that MRS-assessed GABA levels play a pivotal role in various domains of behavior. Even though some converging patterns emerge, it is challenging to draw comprehensive conclusions due to differences in behavioral task paradigms, targeted brain regions of interest, implemented MRS techniques and reference compounds used. Across all studies, the effects of GABA levels on behavioral performance point to generic and partially independent functions that refer to distinctiveness, interference suppression and cognitive flexibility. On one hand, higher baseline GABA levels may support the distinctiveness of neural representations during task performance and better coping with interference and suppression of preferred response tendencies. On the other hand, lower baseline GABA levels may support a reduction of inhibition, leading to higher cognitive flexibility. These effects are task-dependent and appear to be mediated by age. Nonetheless, additional studies using emerging advanced methods are required to further clarify the role of MRS-assessed GABA in behavioral performance.

Abbreviations: GABA, γ-aminobutyric acid; ACC, anterior cingulate cortex; ATL, anterior temporal lobe; Cr, creatine; CSF, cerebrospinal fluid; dACC, dorsal anterior cingulate cortex; DLPFC, dorsolateral prefrontal cortex; FEF, frontal eye field; Glu, glutamate; Gln, glutamine; GM, gray matter; IFG, inferior frontal gyrus; IOG, inferior occipital gyrus; LICI, long-interval intracortical inhibition; MRS, magnetic resonance spectroscopy; MRSI, magnetic resonance spectroscopic imaging; MEGA-PRESS, Meshcher-Garwood Point-Resolved Spectroscopy; MEGA-sLASER, Meshcher-Garwood -semi-localized by adiabatic selective refocusing; MoCA, Montreal Cognitive Assessment; NAA, N-acetylaspartate; OCC, occipital cortex; PCC, posterior cingulate cortex; PET, positron emission tomography; PFC, prefrontal cortex; PPC, posterior-parietal cortex; Pre-SMA, pre-supplementary motor area; M1, primary motor cortex; SICI, short-interval intracortical inhibition; SM1, sensorimotor cortex; STN, subthalamic nucleus; STG, superior temporal gyrus; tCr, total creatine; TMS, transcranial magnetic stimulation; 2ptD, two-point discrimination; WAIS, Wechsler Adult Intelligence Scale; WCST, Wisconsin Card Sorting Test; WM, white matter.

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1. Introduction

In daily life, we continuously deal with external stimuli from the environment or rely on internal stimuli based on our intentions to generate contextually appropriate behavioral responses. The ability to (re)shape our behavior through experience depends on plastic processes in the brain that are contingent upon modulation of neural excitation and inhibition. Both in vivo and in vitro evidence from animal studies has demonstrated that excitatory and inhibitory processes are instrumental to perceptual (Mowery et al., 2019; Stange et al., 2013), motor (Kida and Mitsushima, 2018) and cognitive (Cunha-Rodrigues et al., 2018) task performance and learning. Of particular interest is the increasing evidence that an imbalance between inhibitory and excitatory processes may lead to motor and cognitive disabilities in humans, such as impaired social behavior and altered tactile perception in autism spectrum disorder (Cochran et al., 2015; Puts et al., 2017; Sapey-Triomphe et al., 2019), general cognitive decline in schizophrenia (Reid et al., 2019; Rowland et al., 2016) and recovery of impaired motor and language function in stroke patients (Blicher et al., 2015). As γ-aminobutyric acid (GABA) and Glutamate (Glu) are the major inhibitory and excitatory metabolites in the brain, respectively, both play a pivotal role in coordinating neural functions supporting performance in various behavioral domains in health and disease.

The development of neuroimaging and neurostimulation techniques has made it possible to investigate GABA in vivo. In human studies, at least three non-invasive approaches have been employed to measure GABAergic function directly or indirectly. Transcranial magnetic stimulation (TMS) can be used to assess the level of intracortical inhibition (Kujirai et al., 1993), positron emission tomography (PET) allows for detection of $GABA_A$ receptor availability and magnetic resonance spectroscopy (MRS) enables quantification of local GABA levels in specific brain regions. Notably, these methods are complementary and explore different mechanisms and/or expressions of the GABAergic system. Paired-pulse TMS identifies short-interval intracortical inhibition (SICI; short stimulation intervals) and long-interval intracortical inhibition (LICI; long stimulation intervals), which are thought to reflect $GABA_A$ and $GABA_B$ receptor-mediated synaptic activity, respectively (Kobayashi and Pascual-Leone, 2003). PET can trace the distribution and occupancy of $GABA_A$ receptors by collecting signals from the radioactive tracer via injection of a compound with radioactively labeled ligands, which can bind to $GABA_A$ receptors (Heiss and Herholz, 2006). MRS for quantification of GABA has been developed rapidly since its advent and has been applied in many fields, including, but not limited to, the study of the mechanisms underlying various human behaviors and pathological conditions. In the central nervous system, GABA exists in two major distinct intracellular pools, i.e., a cytoplasmic pool and a vesicular pool. In addition to intracellular GABA, extracellular GABA also exists which acts on extra-synaptic $GABA_A$ receptors. While MRS is capable of precise detection of GABA in the voxel of interest, it is noteworthy to add that it cannot distinguish between different pools of GABA (Puts and Edden, 2012; Stagg, Bachtiar, and Johansen-Berg, 2011b). So far, studies investigating the associations between MRS-assessed GABA levels and TMS-assessed GABA measures have reported mixed findings (Harris et al., 2021; Stagg et al., 2011b). Furthermore, possible associations between TMS, PET, and MRS of GABA measures, are currently being investigated and seem to point to rather distinct underlying processes (Cuypers et al., 2021). Here, we focus on reviewing the studies that used the MRS technique (Section 2. Magnetic resonance spectroscopy) in evaluating inhibitory functions in relation to behavior.

From the perspective of MRS, GABA levels have been associated with various types of behavior, for example, perceptual acuity (Edden et al., 2009), motor response performance (Kolasinski et al., 2017) and executive function (Marsman et al., 2017). Furthermore, expanding abilities and enhancing skills through short-term learning have been reported to depend on the modulation of GABA levels in task-related brain areas (Bezalel et al., 2019; Frangou et al., 2019; Kolasinski et al., 2019). Across larger time scales (up to lifetime development), age-related changes/differences in brain GABA levels have been implicated in the decline of various behaviors, such as inhibitory control and other higher cognitive functions (Hermans et al., 2018; Marenco et al., 2018; Porges et al., 2017; Simmonite et al., 2019). However, there is inconsistency in the literature with respect to regional specificity, the role of GABA in behavior, and whether higher GABA levels are associated with better or worse performance. In sum, although the role of the GABAergic signaling system in various behavioral conditions remains elusive, accumulating evidence has provided first insights into the associations between MRS-assessed GABA levels and behavioral performance as well as training-induced behavioral changes in different task settings.

The current review explores the relationship between MRS-assessed GABA levels at baseline in specific brain areas and a broad repertoire of behaviors including perceptual, motor and cognitive performance in humans. Associations between intervention-induced dynamic changes in GABA levels and performance or learning outcome will not be addressed. Given the potential interactions and/or balance between GABA and Glu, the associations between Glu and behavior are occasionally reported, depending on the available literature. Overall, we aim for a deeper understanding of the potential role of MRS-assessed baseline GABA levels as predictors of behavioral performance. Following the PRISMA guidelines (Moher et al., 2009), we have selected the relevant studies published before April, 2021 using PubMed, Web of Science and Embase databases. Because of the broad scope of this review, the detailed keywords, synonyms, inclusion and exclusion criteria used in the search strategy are listed in the supplementary materials. Reference lists of retrieved articles have also been manually screened for additional relevant studies.

2. Magnetic resonance spectroscopy (MRS)

Proton magnetic resonance spectroscopy (^{1}H MRS) is a valuable non-invasive neuroimaging technique to detect metabolites in the brain and has become an often-used tool to quantify the concentrations of MRS-visible neuro-metabolites. As a result of developments in MR field strength, detection sequences and data analysis methods, advanced MRS techniques can reliably and efficiently detect the concentration of metabolites in a specific brain region, including glutamate (Glu), glutamine (Gln), GABA, Glx (Glu+Gln), N-acetylaspartate (NAA) and creatine (Cr), (for a review, see Puts and Edden, 2012). There are two main types of MRS methods: (i) single-voxel MRS and (ii) multiple-voxel MRS, also referred to as magnetic resonance spectroscopic imaging (MRSI) (Posse et al., 2013). Single-voxel MRS can detect concentrations of neuro-metabolites in a circumscribed locus of the brain. Alternatively, MRSI provides the opportunity to measure the concentrations of metabolites in numerous regions at once. Nevertheless, MRSI for GABA is not yet widely available and the accuracy of determining GABA levels with the current MRSI methods remains elusive at present.

^{1}H MRS is based on the notion that radiofrequency signals emitted from the hydrogen nuclear spins are chemical-specific and appear as different peaks on the spectrum. The difference in MRS-detected signals arising from hydrogen protons in different chemical environments is called the chemical shift and different compounds have peaks at fixed relative chemical shifts. However, with limited separation and splitting of the metabolite peaks, quantification of metabolites with relatively low concentration is still difficult as a result of low signal-to-noise ratio and overlap with other abundant metabolites (Harris et al., 2017). Indeed, GABA concentrations are relatively low and are masked by more highly concentrated metabolites such as Cr (Mullins et al., 2014), making it challenging to quantify reliably with a standard single-voxel technique. In current MRS practice, different sequences including PRESS, SPECIAL, and J-editing sequences such as MEGA-PRESS, etc., have been developed and applied to detect GABA levels at 3T. Among these, the MEGA-PRESS sequence (Mescher et al., 1998) has become the

most commonly used sequence as it has been shown to reliably estimate GABA levels through simplifying the spectrum using editing (Harris et al., 2017). The MEGA-PRESS sequence is a J-difference edited technique that can be tailored to GABA and utilizes two interleaved datasets within a single acquisition: (i) an editing inversion pulse at 1.98 ppm (denoted as 'on' pulse) and (ii) an inversion pulse elsewhere (denoted as 'off' pulse). The effect of this 1.9 ppm editing pulse is principally limited to the GABA spectrum, so the subtraction of the ON spectrum from the OFF spectrum removes the Cr peak and reserves the GABA peak. Although the GABA peak can be distinguished from other neurochemicals with an overlapping chemical shift with this sequence, the peak faces around 40–60% signal contamination from co-edited macromolecules. Therefore the obtained GABA levels with the contribution of macromolecules are commonly referred to as GABA+ (Mullins et al., 2014). Although prospective or retrospective frequency correction can be easily applied to improve the quality of spectra obtained from an unedited MRS sequence, it is not easily achieved in a J-difference edited method. In addition, the J-difference edited MRS method is also more sensitive to frequency drift as it may introduce subtraction artifacts and changes in editing efficiency of GABA and macromolecules (Evans et al., 2013; Harris et al., 2014). In addition to GABA, MEGA-editing also reveals a Glx peak, consisting of combined glutamate + glutamine, which is often interpreted as a marker of excitation, although this interpretation should be approached with caution (Lee and Sherman, 2009). The development of higher magnetic field strengths (7T or higher) has resulted in more precise quantifications of metabolites through improving signal-to-noise ratio and spectral dispersion (Stephenson et al., 2011). However, due to the loss of editing efficiency of the MEGA-PRESS sequence in the 7T MR environment (Edden and Barker, 2007), recent studies have begun to apply other sequences such as the MEGA-semi-localized by adiabatic selective refocusing (MEGA-sLASER) sequence in the ultra-high magnetic fields (Andreychenko et al., 2012).

The reliable quantitation approaches make use of either external or internal references with known concentrations to reduce the effect of arbitrary inter-scan variations. Because systematic errors can occur due to inhomogeneities of both the B0 and B1 magnetic fields when using an external reference, recent studies tend to choose internal references, whose signal is obtained from the same voxel and in the same way as the target metabolite (Gasparovic et al., 2006). Ideally, the concentration of an internal reference standard metabolite should be constant across various physiological conditions (Christiansen et al., 1993). For example, water is commonly used as an internal reference due to its small variation in various conditions as well as easy and accurate determination (Barker et al., 1993; Christiansen et al., 1993). Besides water, NAA and total Cr (tCr: creatine + phosphocreatine) have also been used as reference standards for estimating GABA concentrations. Cr has the benefit that its peak lines up with the peak location of the GABA signal at 3 ppm. NAA is the largest concentration metabolite signal whereas unsuppressed water has the largest SNR but requires additional water-unsuppressed scans. In a small sample size, the measure of GABA/tCr was shown to have less inter- and intra-subject variability compared with the measure of GABA/water (Bogner et al., 2010). However, a recent multi-center study showed that the variation in the measure of GABA/water was similar to GABA/tCr measurement (Mikkelsen et al., 2019). The optimal reference metabolite may alter according to the participants selected for the study and the conditions. For example, tCr may not be a good reference option for clinical conditions since it may not be stable (Gruber et al., 2003).

To improve the quality of spectra, the signal-to-noise ratio must be maximized (Mikkelsen et al., 2018a). From the perspective of space and time, the signal-to-noise ratio increases with the use of bigger voxels or longer acquisition times, typically requiring a volume of around $3 \times 3 \times 3$ cm^3 (Mullins et al., 2014) and corresponding acquisition times. However, a good signal-to-noise ratio is normally achieved at the sacrifice of temporal resolution and anatomical specificity. Given that these large voxels inevitably contain mixed compositions of gray matter (GM), white matter (WM) and cerebrospinal fluid (CSF), and GABA concentrations are reported to be higher in GM compared with WM and negligible in CSF in the MRS studies (Bhattacharyya et al., 2011; Glaeser and Hare, 1975; Manyam et al., 1980), it is important to take tissue composition into account when obtaining optimal estimates (Harris et al., 2015).

Although there is no universally acknowledged methodology for the ideal tissue correction (Harris et al., 2015; Choi et al., 2021; Peek et al., 2020), the success of tissue corrected estimates is primarily determined by the accurate measurement of GM, WM and CSF fractions, water and GABA relaxation times for each sub-tissue, and MR visible water and GABA concentrations for each sub-tissue (Harris et al., 2015). It has been recommended that for referencing relative to tCr or NAA, no such tissue correction is required, whereas for water it is strongly recommended (Lin et al., 2021). Alternatively, tissue composition can be accounted for statistically (Mullins et al., 2014). Currently, the assumption commonly used when applying tissue correction for the referenced data is that (i) CSF needs to be accounted for, and that (ii) the concentration ratio of GABA is approximately 2:1 between GM and WM (Harris et al., 2015; Mikkelsen et al., 2016). Furthermore, GM-only correction should not be applied (Harris et al., 2015; Peek et al., 2020). According to a recent meta-analysis study, it is speculated that the potential effect of tissue composition might be limited for healthy young participants because brain atrophy at such ages hardly exists (Porges et al., 2021).

As the tissue correction and choice of reference metabolites impact the interpretation of the results, we have decided to provide information regarding reference compounds and tissue correction along with the MR techniques to facilitate comparison across studies (see Table 1). Of note, in the following sections, we will use the terms GABA levels or GABA concentrations interchangeably to represent MRS-assessed GABA+ quantities regardless of reference compound (details can be found in Table 1). In addition, because of the relatively big size of the MRS voxels studied, the voxel targeted at the hand knob area in the primary motor cortex (M1) often has a significant overlap with the somatosensory area (S1). Therefore, we will denote this as the sensorimotor cortex (SM1).

3. MRS-assessed GABA concentrations during rest and their associations with behavioral performance

Numerous studies have linked MRS-assessed GABA levels at rest, often referred to as *'baseline'* or *'resting'* GABA levels, with the accuracy or efficiency of performance on various types of tasks. The reported behavioral metrics and their associated brain areas are visualized in Fig. 1. Although some tasks rely on a combination of perceptual, motor and cognitive abilities, we will first classify the evidence based on one of these three major behavioral domains and then separately discuss the reported findings according to the main task requirements. Our ultimate goal is to formulate some generic hypotheses about GABA's potential role based on converging evidence across different task domains.

3.1. Associations between baseline GABA levels and perceptual performance

We consistently receive, discriminate and process visual, tactile, proprioceptive and auditory information to make appropriate decisions. For example, when grasping an object, we look at the object and predict its size in order to initiate a suitable hand posture. Meanwhile, we touch and evaluate the surface's texture to apply sufficient force to prevent the object from slipping through our fingers. GABA is thought to play a critical role in visual (Song et al., 2017), tactile (Puts et al., 2011), auditory (Razak and Fuzessery, 2009) as well as multisensory processing (Balz et al., 2016). Across these modalities, existing studies focusing on the association between the MRS-assessed GABA levels in a task-dependent brain area and perceptual performance will be further discussed according to whether perceptual acuity or interference suppression is the key requirement in these tasks.

Table 1
Summary of studies focusing on associations between baseline GABA and behavior

Author year	Sample size	Strength Coil Sequence	Region Voxel size (mm^3)	Metabolite /reference compound	Tissue Correction[1]	Software	Task	Behavioral measures	Modulation & Correlation[2]
Perceptual performance									
Cook et al. (2016)	9 H	3T Coil: NS MEGA-PRESS	OCC 30 × 35 × 20	GABA /water	NS	Gannet	visual intelligence in WAIS visual suppression task	(1) scores (2) surround suppression index	(r = 0.83, p = 0.0054) measure (1) & OCC GABA (r = 0.88, p = 0.0017) measure (2) & OCC GABA
Dobri and Ross (2021)	19 Y 19 O	3T 32-channel MEGA-PRESS	bilateral AC 25 × 25 × 25	GABA /water, Cr	Harris et al. (2015)	Gannet and in-house scripts	hearing threshold QuickSIN test	(1) hearing threshold (2) SIN loss	In older adults, decreased averaged GABA in bilateral AC & elevated measure (1) a negative association between right AC GABA & measure (2)
Edden et al. (2009)	13 H	3T 8-channel MEGA-PRESS	OCC 30 × 30 × 30	GABA /water	NS	in-house scripts	a visual orientation discrimination task	(1) discrimination threshold	(r = −0.65, p < 0.015) measure (1) in oblique condition & OCC GABA (r = −0.39, p = 0.2) measure (1) in vertical condition & OCC GABA
Heba et al. (2016)	18 H	3T 32-channel MEGA-PRESS	bilateral SM1 30 × 30 × 30	GABA /water	CSF Correction	Gannet	Electrical repetitive sensory stimulation 2ptD of the index finger	(1) 2ptD before (2) 2ptD after (3) learning gain: difference (1) and (2)	(r = 0.74, p < 0.001) measure (3) & left SM1 GABA levels (r = −0.76, p < 0.001) measure (2) & left SM1 GABA levels
Kihara et al. (2016)	22 H	3T 12-channel GABA editing	left PFC, right PPC, OCC 30 × 30 × 30	GABA /Cr	NS	Gannet and in-house scripts	an attentional blink task	(1) first target accuracy (2) attentional blink magnitude	(r = −0.62, p < 0.003) measure (2) & left PFC GABA. (r = 0.51, p < 0.02) measure (2) & right PPC GABA. (r = 0.54, p < 0.01) measure (1) & left PFC GABA.
Kolasinski et al. (2017)	11 H	7T 32-channel sLASER	left SM1 and OCC 20 × 20 × 20	GABA Glu /tCr	GM Correction	LCModel	a tactile temporal order judgment task	(1) just noticeable difference	(r = −0.678, p = 0.02) measure (1) & SM1 GABA levels
Kondo et al. (2017)	22 H	3T 12-channel GABA editing	left AC, left IFG, left PFC, ACC 30 × 30 × 30	GABA Glx /water	NS	Gannet and in-house scripts	a multi-stability task a response inhibition task	(1) switching patterns	measure (1) & AC Glx and IFG GABA
Kondo and Kochiyama (2018)	38 H	3T 12-channel MEGA-PRESS	right AC, PFC, ACC, ventrolateral OCC 30 × 30 × 30	GABA /water	NS	Gannet	auditory streaming visual plaids	(1) auditory volitional control (2) visual volitional control	(r = 0.35, p < 0.05) measure (1) & AC GABA (r = 0.31, p < 0.10) measure (2) & ventrolateral OCC GABA
Kondo et al. (2018)	36 H	3T 12-channel MEGA-PRESS	right AC, PFC, PPC, ventrolateral OCC 30 × 30 × 30	GABA Glx /water	NS	TARQUIN	auditory streaming visual plaids	(1) auditory duration (2) visual duration (3) volitional auditory control	(r = 0.59, p < 0.01) measure (1) & AC GABA/Glx (r = 0.57, p < 0.01) measure (2) & ventrolateral OCC GABA/Glx (r = 0.39, p < 0.05) measure (3) & PPC GABA/Glx
Maeshima et al. (2018)	23 H	3T 64-channel MEGA-PRESS	bilateral STG 25 × 30 × 25	GABA /Cr & water	NS	Gannet	an absolute pitch task	(1) accuracy	[r (21) = −0.45, p = 0.022] measure (1) & left STG GABA levels

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Table 1 (*continued*)

Author year	Sample size	Strength Coil Sequence	Region Voxel size (mm^3)	Metabolite/ reference compound	Tissue Correction[1]	Data analysis Software	Task	Behavioral measures	Modulation & Correlation[2]
Mikkelsen et al. (2018a, 2018b)	14 M	3T 32-channel MEGA-PRESS	right SM1, OCC 30 × 30 × 30	GABA /water	Harris et al. (2015)	Gannet	orientation discrimination tactile amplitude discrimination tactile frequency discrimination	(1) amplitude discrimination threshold (2) frequency threshold (3) oriental threshold	($r = -0.63$, $p = 0.03$) measure (1) & SM1 GABA ($r = -0.62$, $p = 0.02$) measure (2) & SM1 GABA ($r = -0.59$, $p = 0.05$) measure (3) & OCC GABA
Pitchaimuthu et al. (2017)	20 Y 20 O	3T 32-channel MEGA-PRESS	OCC and right DLPFC 30 × 25 × 20	GABA Glx /water & tCr	Harris et al. (2015)	Gannet	a binocular rivalry task a spatial motion suppression task	(1) median duration (2) switches	($r = 0.35$, $p = 0.03$) measure (1) & OCC GABA levels in all participants ($r = 0.36$, $p = 0.03$) measure (2) & OCC GABA levels in all participants
Puts et al. (2011)	15 H	3T 8-channel MEGA-PRESS	right SM1 and OCC 30 × 30 × 30	GABA /water	CSF Correction	in-house scripts	a tactile frequency discrimination task	(1) frequency threshold	($r = -0.58$, $p < 0.05$) measure (1) & SM1 GABA ($r = -0.04$, $p > 0.5$) measure (1) & OCC GABA
Sandberg et al. (2016)	37 M	3T Coil: NS MEGA-PRESS	large OCC 30 × 30 × 30 right small OCC 18 × 18 × 25	GABA /Cr	both GM Correction and no tissue correction	jMRUI	a structure from motion task	(1) percept duration	a positive association between measure (1) & right OCC GABA
Song et al. (2017)	30 M	3T Coil: NS MEGA-PRESS	parietal cortex 20 × 20 × 20 OCC 30 × 30 × 30	GABA /Cr	NS	jMRUI	visual contextual illusion suppression	(1) size, (2) oriental and (3) bright illusion suppression	($r = 0.395$, $p = 0.031$) measure (1) & parietal GABA ($r = 0.367$, $p = 0.046$) measure (2) & OCC GABA
Sumner et al. (2010)	12 H	3T a phase-array MEGA-PRESS	FEF and OCC 30 × 30 × 30	GABA /water	CSF Correction	in-house scripts	a saccade distraction task	(1) latency increase	($r = -0.76$, $p = 0.004$) measure (1) & FEF GABA levels
van Loon et al. (2013)	18 M	3T 8-channel MEGA-PRESS	OCC 30 × 25 × 20 right DLPFC 30 × 25 × 20	GABA Glx /tCr	GM Correction	LCModel	a binocular rivalry a motion blindness a structure from motion task	(1) mean duration (2) mean invisible duration (3) mean duration	a positive correlation between measure (1), (2), (3) & OCC GABA no association with DLPFC GABA
Motor performance									
Cassady et al. (2019)	21 Y 21 O	3T 8-channel MEGA-PRESS	left and right SM1 30 × 30 × 30	GABA /water	Harris et al. (2015)	Gannet	9-hole pegboard grip strength 2-min walk endurance some vibrotactile threshold tasks	(1) overall performance of all tasks	($r = 0.32$, $p = 0.046$) measure (1) & GABA levels across all participants ($r = 0.48$, $p = 0.031$) older adult group alone ($r = -0.14$, $p = 0.55$) younger adult group alone.
Chalavi et al. (2018)	32 Y 28 O	3T 32-channel MEGA-PRESS	OCC and left SM1 30 × 30 × 30	GABA /water	Harris et al. (2015)	Gannet	a bimanual coordination task	(1) initial error rate (2) retention error	positive association between measure (1) & baseline SM1 GABA levels
Maes et al. (2021)	29 Y 30 O	3T 32-channel MEGA-PRESS	bilateral SM1, SMA 30 × 30 × 30 bilateral PMd, bilateral DLPFC, 40 × 25 × 25	GABA /water	Harris et al. (2015)	Gannet	Purdue Pegboard a bimanual coordination task finger tapping tasks	(1) number of inserted pins (2) number of corrected types (3) error scores	($\chi 2 = 7.97$, $p = 0.005$) higher overall GABA levels & better measure (1) in older adults ($\chi 2 = 9.48$, $p = 0.002$) higher overall GABA levels & poorer

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Table 1 (*continued*)

									measure (3) in young adults
Stagg et al. (2011a)	12 H	3T coil: NS PRESS MEGA-PRESS	left SM1 20 × 20 × 20 OCC 20 × 30 × 20	GABA Glx, Cr /NAA	GM correction	jMRUI	a sequence tapping learning task	(1) block 1 RT (2) block 15 RT (3) block 10–14 RT (4) learning gain	($r = 0.64$, $p = 0.03$) the measure (1) baseline SM1 GABA levels
Cognitive performance									
Cheng et al. (2017)	19 H	3T 32-channel MEGA-PRESS	bilateral STG 20 × 25 × 25	GABA /water	CSF and GM correction	in-house scripts	an auditory Go/ No-go task	(1) accuracy (No-go)	($r = 0.547$, $p = 0.032$ measure (1) & right STG GABA levels
Cohen Kadosh et al. (2015)	14 adults 14 children	3T 32-channel SPECIAL	left IFG, right IPS and right IOG 20 × 20 × 20	GABA Glu NAA /tCr	NS	LCModel	Cambridge memory test for faces a visual-spatial working memory	(1) Z-scores in face memory test (2) Z-scores in working memory	[$r (14) = 0.650$, $p = 0.012$) measure (1) & IFG Glu/ GABA in children, [$r (10) = -0.84$, $p = 0.002$] measure (2) & IOG Glu/ GABA in the adults
Author year	**Sample size**	**Strength Coil Sequence**	**Region Voxel size (mm^3)**	**Metabolite/ reference compound**	**Tissue Correction[1]**	**Data analysis Software**	**Task**	**Behavioral measures**	**Modulation & Correlation[2]**
de la Vega et al. (2014)	32 H	3T 8-channel MEGA-PRESS PRESS	left IFG 24.3 × 35.6 × 22.7 left MFG 23.6 × 34.4 × 25.4	GABA Glu /water	GM Correction	LCModel GE's SAGE	Selection Tasks General Executive Function Tasks	(1) Z-score (RT)	[$\beta = -0.49$, $t (21) = -2.48$, $n = 23$, $p = 0.02$] measure (1) and the GABA/ Glu ratio in PFC
Del Tufo et al. (2018)	69 children	4T H-tuned surface coil J-editing sequence	OCC 30 × 30 × 15	GABA, Cho, Glu, NAA /Cr	NS	in-house scripts	Cross-Modal language integration task	(1) cross-modal RT	lower measure (1) & lower OCC GABA
Haag et al. (2015)	22 APT 18 non-trainees	3T 32-channel MEGA-PRESS	bilateral striatum 30 × 30 × 25	GABA /tCr	NS	LCModel	a modified Simon task (crossed or parallel hands, correspondence or not)	(1) RT (2) accuracy	measure (2) in crossed hand and incongruent condition & averaged GABA in bilateral stratum in all participants ($r = 0.4$, $p < 0.2$), in trainee ($r = 0.6$, $p < 0.01$), in non-trainee ($r = 0.72$, $p < 0.01$)
Hermans et al. (2018)	30 Y 29 O	3T 32-channel MEGA-PRESS	left SM1, pre-SMA, bilateral striatum, OCC 30 × 30 × 30, right IFG, 40 × 25 × 25	GABA /water	Harris et al. (2015)	Gannet	a stop signal task	(1) RT	($r = -0.459$, $p = 0.031$) measure (1) & pre-SMA GABA in older adults ($r = 0.185$, $p = 0.387$) measure (1) & pre-SMA GABA in young adults
Jung et al. (2017)	20 H	3T 32-channel MEGA-PRESS	left ATL 35 × 25 × 15 OCC 30 × 30 × 30	GABA Glx /NAA	NS	jMRUI	a semantic association task a pattern matching task	(1) semantic accuracy (2) pattern accuracy	($r = 0.43$, $p < 0.05$) measure (1) & ATL GABA levels
Koizumi et al. (2018)	41 H	3T 12-channel MEGA-PRESS	ACC, DLPFC, SMA 30 × 30 × 30	Glx/GABA	NS	TARQUIN	an auditory Go/ No-go task	(1) error rate (No-go) (2) accuracy rate (Go)	($r = 0.530$, $p = 0.0009$) measure (1) & DLPFC E/I ratio no distractors ($r = 0.353$, $p = 0.044$) measure (2) and ACC E/I ratio with distractors positive association between WCST scores performance & dACC GABA
Marenco et al. (2018)	171 H	3T, quadrature PRESS-based J-editing	dACC (mPFC), right frontal white matter 20 × 20 × 45	GABA /Cr & water	CSF Correction	In-house scripts	verbal, working, visual memory processing speed, WCST, digit span	scores of each task	
Marsman et al. (2017)	19 H	7T 32-channel MEGA-	Glu: PFC, OCC 20 × 20 × 20 GABA: PFC,	GABA Glu /Cr & water	CSF Correction	LCModel	Cognitive: WAIS	(1) working memory index (2) TIQ, VIQ, PIQ, PRI, VCI	($r = -0.80$, $p = 0.01$) measure (1) & frontal GABA/ Glu ratio

(*continued on next page*)

Table 1 (*continued*)

		sLASER sLASER	OCC 25 × 25 × 25						(r = −0.79, p < 0.004) measure (1) & OCC Glu levels
Porges_et al (2017)	89 O	3T 32-channel MEGA-PRESS	frontal and posterior midline cortex 30 × 30 × 30	GABA /water	CSF Correction	Gannet	MoCA	(1) MoCA score	[F (1,87) = 18.95, p < 0.001] measure (1) & frontal GABA, [F (1,88) = 5.267, p = 0.07] measure (1) & posterior GABA
Nakai and Okanoya (2016)	28 H	3T 64-channel MEGA-PRESS	bilateral IFG 20 × 20 × 20	GABA /Cr & water	NS	Gannet	a letter and category fluency task	(1) letter score (2) category score	(r = −0.48, p = 0.017) measure (2) & left IFG GABA levels
Quetscher et al. (2015)	40 H	3T, 32-channel MEGA-PRESS PRESS	left stratum right stratum 30 × 30 × 25	GABA, NAA, Glx /tCr	GM correction	LCModel	a standard Go/ No-go task	(1) RT (Go) (2) false rate (No-go)	(r = −0.541, p < 0.01) measure (2) & striatal GABA levels
Sandberg et al. (2014)	36 M	3T Coil: NS MEGA-PRESS	OCC 30 × 30 × 30 parietal cortex 20 × 20 × 20	GABA /Cr	NS	jMRUI	Cognitive failures questions	(1) scores	(r (31) = −0.417, p = 0.032) measure (1) & OCC GABA (r (30) = −0.005, p = 0.98) measure (1) & parietal GABA
Author year	**Sample size**	**Strength Coil Sequence**	**Region Voxel size (mm^3)**	**Metabolite/ reference compound**	**Tissue Correction[1]**	**Data analysis Software**	**Task**	**Behavioral measures**	**Modulation & Correlation[2]**
Schmitz et al. (2017)	24 H	3T 32-channel 2D J-PRESS	hippocampus 10 × 10 × 40 DLPFC, OCC 25 × 25 × 25	GABA Glu /Cr	NS	ProFit algorithm	a Think/No-think task a Stop Signal task	(1) forgetting in No-Think condition (2) RT in stop signal	(r = 0.45, p < 0.05, n = 18) measure (1) & hippocampus GABA
Scholl et al. (2017)	27 H	3T 32-channel MEGA-PRESS	dACC 20 × 20 × 20	GABA Glu /tCr	GM and WM correction	LCModel	multi-dimensional learning task	(1) use of learnt information	(p = 0.039) negative association between measure (1) & dACC glutamate (p = 0.05) positive association between measure (1) & dACC GABA
Silveri et al. (2013)	30 adolescents 20 adults	4T volumetric MEGA-PRESS	ACC 20 × 20 × 30 POC 20 × 20 × 30	GABA /Cr	NS	LCModel	a modified Stroop task a Go/No-go task	(1) accuracy rate (No-go)	[r (49) = 0.282, p = 0.026) measure (1) & ACC GABA levels
Simmonite et al. (2019)	17 Y 18 O	3T 32-channel PRESS MEGA-PRESS	OCC 30 × 30 × 25	GABA, Glx, NAA, Cho, Myo /Cr	NS	LCModel Gannet	11 tasks assessing fluid processing ability	(1) Z-scores	[t (31) = 1.84, p < 0.05] measure (1) & OCC GABA in combined groups
Spurny et al. (2020)	20 H	3T 64-channel 3D-MRSI MEGA-LASER	hippocampus, insula, thalamus	GABA Glx tNAA /tCr	NS	in-house scripts	an associative facial learning task	(1) IRS (2) FRS (3) RI	(r = 0.69, p = 0.013) measure (1) & hippocampal GABA levels
Takei et al. (2016)	20 H	3T 12-channel MEGA-PRESS	pg-ACC, mid-ACC, OCC 30 × 20 × 20	GABA Glx /Cr	NS	jMRUI	a working memory task (N-back paradigm)	(1) RT, (2) correct rate, (3) relative (1), (4) relative (2)	(r = −0.50, p = 0.031) measure (4) & pg-ACC GABA (r = −0.67, p = 0.009) measure (4) & OCC GABA
Yoon et al. (2016)	23 H	3T 32-channel WIP	left DLPFC 30 × 15 × 35 OCC 35 × 30 × 25	GABA /tCr	NS	jMRUI	a working memory task	(1) accuracy change between one face and two faces	[r (23) = −0.564, p = 0.015] measure (1) & DLPFC GABA

2ptD, two-point discrimination; AC, auditory cortex; ACC, anterior cingulate cortex; APT, airplane pilot trainees; ATL, anterior temporal lobe; Cho, choline; Cr, creatine; CSF, cerebrospinal fluid; dACC, dorsal anterior cingulate cortex; DLPFC, dorsolateral prefrontal cortex; E/I, excitation/inhibition; FEF, frontal eye field; FRS, final-retrieval-success; GABA, γ - aminobutyric acid; Glu, glutamate; Glx, glutamate and glutamine; GM, gray matter; H, healthy subjects; IFG, inferior frontal gyrus; IOG, inferior occipital gyrus; IPS, intraparietal sulcus; IRS, initial-retrieval-success; M, male subjects; MEGA-sLASER, Meshcher-Garwood-semi-localized by adiabatic selective refocusing; MEGA-PRESS, Meshcher-Garwood Point Resolved Spectroscopy; MFG, middle frontal gyrus; MRSI, magnetic resonance spectroscopic imaging; MoCA, Montreal Cognitive Assessment; Myo, myoinositol; NS, not specified; NAA, N-acetylaspartate; O, older subjects; OCC, occipital cortex; PFC, prefrontal cortex; pg-ACC, perigenual anterior cingulate cortex; PIQ, performance intelligence quotient; POC, parietal-occipital cortex; PPC, posterior parietal cortex; pre-SMA, pre-

supplementary motor area; PRESS, Point Resolved Spectroscopy; PRI, perceptual reasoning index; RI, retrieval improvement; RT, reaction time; sLASER semi-localized by adiabatic selective refocusing; SIN, speech-in-noise; SM1, sensorimotor cortex; SMA, supplementary motor area; SPECIAL, spin-echo full-intensity acquired localized; STG, superior temporal gyri; T, Tesla; tCr, total creatine; TIQ, total intelligence quotient; VCI, verbal comprehension index; VIQ, verbal intelligence quotient; WAIS, Wechsler Adult Intelligence Scale; WCST, Wisconsin Card Sorting Test; WIP, Works-in-Progress; Y, young subjects.

[1] The correction equations from (Harris et al., 2015) are with the assumption that GABA levels are twice as high in GM compared with WM and CSF contains no GABA; CSF correction refers to i) a correction method with the assumption that the GABA concentration in GM and WM are the same and CSF contains no GABA, or ii) a correction method based on CSF volume with no detailed information about assumption; GM correction refers to i) a correction method with the assumption that only GM contains GABA, ii) a correction method based on GM volume with no detailed information about assumption, or iii) using GM volume as a covariate during analysis; GM and WM correction refers to using GM and WM volume as covariates during analysis.

[2] Only part of the critical and relevant results was summarized in the column Modulation and Correlation.

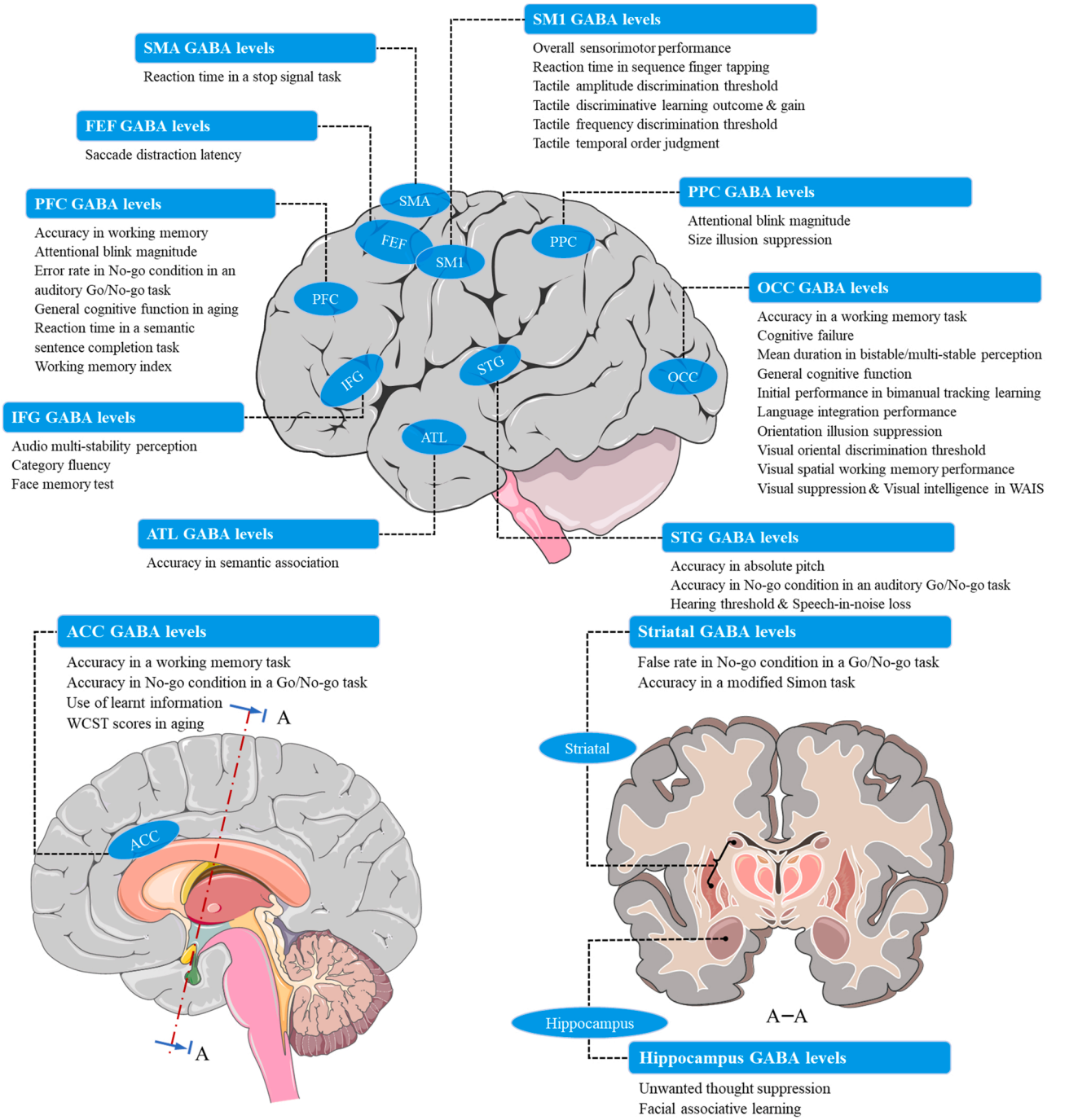

Fig. 1. Reported associations between behavioral metrics and MRS-assessed baseline GABA levels in specific brain areas. ACC, anterior cingulate cortex; ATL, anterior temporal lobe; FEF, frontal eye field; IFG, inferior frontal gyrus; OCC, occipital cortex; PFC, prefrontal cortex; PPC, posterior parietal cortex; SMA, supplementary motor area; SM1, sensorimotor cortex; STG, superior temporal gyrus. Note: studies reporting no association between GABA levels and behavioral measures were not included in this figure. Parts of the figure are adapted from 'Smart Servier Medical Art' (https://smart.servier.com/).

3.1.1. Perceptual discrimination and acuity

Among studies addressing associations between baseline GABA levels in brain regions that process visual, tactile and auditory information and corresponding perceptual discriminative performance or acuity, the occipital cortex (OCC), somatosensory cortex (as part of SM1) and superior temporal gyrus (STG) have attracted significant interest since these are the most dominant sensory processing areas for visual, somatosensory and auditory signals, respectively.

To examine the role of baseline OCC GABA levels in visual discrimination performance, Edden and coworkers (2009) used an orientation discrimination paradigm in which the orientation of an initial stimulus pattern was held at 0° or 45° in vertical or oblique conditions, respectively. The participants judged whether the second pattern was turned clockwise or counterclockwise as compared to the first pattern in both conditions. Hence lower thresholds reflected better visual discriminative performance. Findings revealed that higher baseline OCC GABA levels were correlated with a lower oblique orientation detection threshold, implying better visual orientation-selective performance. This positive association between higher OCC GABA levels and better orientation discrimination ability was further confirmed by Mikkelsen et al. (2018b) using the same task. However, no such relationship was found in the case of vertical discrimination conditions (Edden et al., 2009). Similar to the latter tasks, Kurcyus et al. (2018) also used a visual discrimination task and identified a positive association between higher OCC GABA levels when seeing a flickering checkerboard and better discrimination of tilted angles. Although the role of task-state GABA levels may deviate from that of the resting-state GABA levels, this finding does highlight the beneficial role of higher GABA levels in the separation of visual representations. Besides, higher baseline OCC GABA levels were associated with better scores on visual-spatial performance, as assessed by the subset of the Wechsler Adult Intelligence Scale (WAIS) (Cook et al., 2016).

Regarding tactile discrimination performance, Puts et al. (2011) utilized a tactile frequency discrimination paradigm to investigate the relationship between baseline SM1 GABA levels and vibrotactile perception. Adults were required to indicate which of two presented stimuli had a higher vibration frequency. In line with the results from the visual system, higher baseline SM1 GABA levels were associated with a lower tactile vibration frequency discrimination threshold, indicating that adults with higher baseline SM1 GABA levels were more sensitive to the tactile vibration frequency differences. Moreover, this correlation was successively confirmed in adults (Mikkelsen et al., 2018b) and typically-developing children, while such correlation was not observed in OCC as the control area (Puts et al., 2015, 2017).

Besides tactile frequency discrimination, the association between tactile amplitude discrimination and SM1 GABA levels has also been studied in adults (Mikkelsen et al., 2018b) and typically developing children (Puts et al., 2015). In this paradigm, two tactile stimuli were simultaneously applied to the left index and middle fingers, and the participants were required to indicate which stimuli had a higher amplitude (noticeable amplitude difference). Again, results showed that higher baseline SM1 GABA levels are associated with lower tactile amplitude discrimination thresholds (Mikkelsen et al., 2018b). In addition, the association between tactile amplitude adaptation and SM1 GABA levels was further studied in typically developing children (Puts et al., 2015). Because tactile adaptation processes may diminish the discrimination performance, superior performance against the adaptation was represented by a smaller increase of amplitude detection threshold in the adaptation as compared to the baseline condition. In this study, participants with higher SM1 GABA levels managed to maintain a relatively lower amplitude discrimination threshold with adaptation. Kolasinski et al. (2017) used an order judgment paradigm to study the role of SM1 GABA levels in tactile discrimination acuity. Here, tactile stimuli were sequentially applied to the distal pads of the index and middle fingers of the right hand and participants had to report the position of the stimulus that came first. Combined with a task-related fMRI technique, they found that higher SM1 GABA levels were associated with more selective cortical tuning, which led to better tactile order discrimination ability and enhanced perception, as represented by a lower noticeable order difference. Additionally, Heba and coworkers used repetitive somatosensory stimulation of all fingers of the right hand as part of a perceptual learning paradigm to study tactile learning performance, while the fingers of the left hand served as control. They measured tactile sensitivity using two-point discrimination (2ptD) of the index finger before and after stimulation (pre- and post-test) to reveal learning gains and final performance. Their results showed that both the tactile sensitivity learning gains and final learning outcomes were positively associated with baseline SM1 GABA levels. However, they did not observe an association between baseline SM1 GABA levels and pre-test performance levels (Heba et al., 2016).

Finally, auditory acuity and discrimination performance and their association with GABA levels in auditory cortices in young and aging populations were investigated by Dobri and Ross (2021). Their findings showed that increased hearing thresholds in older adults were associated with decreased GABA levels, yet only when averaged across voxels of bilateral auditory cortices. This suggests a potential role of higher GABA levels in the auditory cortex in hearing sensitivity. Focusing on both young and aging populations, Lalwani et al. (2019) investigated the association between the fMRI-evaluated distinct activation patterns with music and foreign speech stimuli and baseline GABA levels in three main sensory brain areas, i.e., the auditory, visual and sensorimotor cortex. They found that higher GABA levels in the auditory cortex, but not in the visual or sensorimotor regions, were correlated with more distinct neural activation when listening to music and foreign language in older adults. However, contradictory evidence exists for perfect pitch performance (i.e., the capacity to label the pitch of tones without any reference). This ability was negatively associated with GABA levels in the left STG, an associative brain area (Maeshima et al., 2018), whose volume and function have been reported as a marker for perfect pitch (Wengenroth et al., 2014).

To summarize, from the studies addressing associations between baseline GABA levels in the brain regions that process visual, tactile and auditory information and corresponding perceptual discriminative or acuity performance, a consistent picture emerges that supports an association with MRS-assessed GABA levels. Specifically, maintaining appropriate neural suppression levels in primary perceptual processing regions and distinct cortical tuning at rest via high GABA levels may lead to more refined representations that mediate optimal perceptual acuity and sensitivity. We refer to this as the ***GABA-distinctiveness hypothesis*** that apparently applies across different sensory modalities.

3.1.2. Perceptual interference

In the context of this review, interference refers to i) irrelevant representations activated by the task stimuli which are not conducive to the task goal, ii) responses activated by goal-irrelevant stimuli, or iii) internal intrusions unrelated to the task. Accordingly, interference can originate from external (perceptual stimuli) or internal sources (cognitive processes).

3.1.2.1. Perceptual illusions. A perceptual illusion occurs when the brain misinterprets incoming information from one or more sensory modalities (Gregory, 1968). Among different paradigms, 'visual' illusion is the most studied sensory modality. Associations between GABA levels in pertinent brain areas and visual illusions have been studied with the use of images with a specialized structure (Cook et al., 2016), using different backgrounds (Song et al., 2017) or forming bistable or multi-stable perception (Chan et al., 2019; Kondo and Kochiyama, 2018; Kondo et al., 2018, 2017; Pitchaimuthu et al., 2017; van Loon et al., 2013). For example, Cook and coworkers used a visual stimulus with grating patterns, which are known to induce visual surround suppression and less surround contrast, to investigate the association between visual

surround suppression and baseline OCC GABA levels. Participants judged which of the two sequentially presented target stimuli (grating pattern and control) had higher contrast. The visual surround suppression strength was measured by the noticeable difference in contrast threshold between these two images. The findings showed that higher baseline OCC GABA levels were associated with a bigger visual suppression and less contrast, which implies larger image-induced illusions (Cook et al., 2016). Another method to induce visual illusions is to vary the surrounding information that accompanies a central visual target to influence the perception of a target's features such as size, orientation, or luminescence. Using this approach, Song and colleagues showed that higher OCC GABA levels were associated with a bigger magnitude of orientation illusion and higher parietal GABA with a larger magnitude of size illusions (Song et al., 2017). These results indicate a selective role of GABA levels in the perception of different image features. The magnitude of illusions, as compared to the real physical feature, can possibly be considered a contextual response to make a situational decision during complex real-life situations. Accordingly, higher GABA levels may support the suppression of prepotent perceptual representations to enable a contextual/adaptive perception that is specific to the current situation.

On the other hand, bistable or multi-stable perception can be seen as another kind of perceptual illusion. Visual bistable perception is a phenomenon in which an ambiguous visual stimulus is presented and forms two mutually exclusive interpretations in the human brain, such as Rubin's Vase in which two interpretations of the image (vase versus face) alternate spontaneously (Rubin, 1915). One potential hypothesis is that one percept is active while the other one is apparently being suppressed (Alais, 2012). Binocular rivalry is a widely used phenomenon to experimentally study bistable visual perception. Here, separate images with apparent differences in color, texture, etc., are presented to each eye. Studies have revealed that higher baseline OCC GABA levels are associated with both a decreased number of switches between the two images and a longer continuous perceptual duration for one image (Pitchaimuthu et al., 2017; van Loon et al., 2013). This association between higher OCC GABA levels and slower perceptual dynamics was also verified in other phenomena of bistable perception, such as the motion-induced blindness and structure-from-motion (van Loon et al., 2013). In addition, a higher ventrolateral OCC GABA/Glx ratio was found to be associated with longer mean perception duration in visual plaids which is another task assessing bistable vision (Kondo et al., 2018). These findings suggest a role for higher GABA in sensory processing areas for interference suppression. In contrast, visual bistable alternation was not associated with the OCC Glx levels or GABA levels in the dorsolateral prefrontal cortex (DLPFC) (Pitchaimuthu et al., 2017; van Loon et al., 2013). The relation between percept duration and OCC GABA levels was further confirmed by Sandberg et al. (2016). On top of this, they highlighted the importance of the gray matter volume in the superior parietal lobe (which is a higher-order brain area remote from the target brain area) on the relation between OCC GABA levels and percept duration in bistable perception.

However, contradictory evidence also exists, in which neither MRS-assessed GABA nor Glx levels were linked to the perceptual duration in a mixed population of healthy adults and those with migraine (Chan et al., 2019). Here, the GABA-behavior association was not studied in the separate subgroups and thus the migraine subgroup might have confounded the association between GABA and perceptual dynamics. Overall, the dependence of bistable visual perception on OCC GABA levels among the healthy population requires further attention.

Similar to visual perception, neuro-metabolites in the primary auditory cortex have shown associations with individual switch patterns in the context of auditory multi-stability. For example, three or more perceptual organization switches could be produced by listening to a sequence of repeating tone triplets as ABA, where A and B had different frequencies (an auditory streaming paradigm) or through prolonged listening to a repeated word without a pause (verbal transformations). It was found that the individual modality-specific probability of switches between percepts and their duration correlated with Glx (but not GABA) levels in the primary auditory cortex and GABA levels in the inferior frontal gyrus (IFG) (Kondo et al., 2017). It was concluded that a balance between Glx and GABA in different brain areas may affect the perception modality.

To summarize, several studies support associations between MRS-assessed GABA levels in task-relevant brain areas and coping with interference induced by prepotent perceptual representations or competition between ambiguous perceptions. Specifically, lower interference effects, as represented by forming adaptive perceptions and competition resolution, may depend on higher GABA levels in task-related brain areas. We refer to this as the ***GABA interference-suppression hypothesis***. On the one hand, suppression of prepotent perceptual representations and formation of contextual perceptions (based on image structure and layout) appear to rely more on cortical inhibition associated with GABA levels in the primary sensory cortices. Specifically, higher neural inhibitory activity in the primary visual cortex is related to better adaptive perception, as represented by more significant peripheral visual suppression and a higher magnitude of orientation/size illusion (Cook et al., 2016; Song et al., 2017). On the other hand, bistable visual perception is related to GABA levels in the visual cortex (Kondo et al., 2018; Pitchaimuthu et al., 2017; van Loon et al., 2013). This is consistent with previous evidence that brain activity in the primary visual cortex varies with the reported image in multi-stable percepts (Parkkonen et al., 2008). In a similar way, the effects of higher OCC GABA levels on perceptual dynamics of a visual scene may be mediated by better suppression of the competition among perceptual images. In addition, a complex multi-stable auditory paradigm also supports an important role of GABA levels in IFG (Kondo et al., 2017). Accordingly, most studies investigating associations between brain GABA levels and perceptual illusions support the *GABA interference-suppression hypothesis*.

3.1.2.2. Perception and selective attention. Visual masking is a perceptual phenomenon in which visual awareness of a presented target decreases when other objects (the mask) are present in close spatial or temporal vicinity (Enns, Di Lollo, 2000). For example, higher baseline GABA levels in the vicinity of the frontal eye field (FEF), a prefrontal area known to be involved in attentional allocation and eye movement planning, were found to be associated with faster eye motion speed, in other words, less susceptibility to the distractor (Sumner et al., 2010). Interestingly, this relationship was not observed in OCC as the control area.

Kihara et al. (2016) used a rapid sequential visual presentation paradigm with two targets and a number of distractors to assess the relationships between visual masking induced by a short temporal interval and baseline GABA levels within the prefrontal cortex (PFC), posterior-parietal cortex (PPC), and OCC. The difference in the second target's accuracy between short and long intervals within these two targets was referred to as attentional blink magnitude. A smaller magnitude referred to a better visual ability against masking and better selective attention. This phenomenon reflected temporal limitations in the ability to deploy visual attention. No link between baseline OCC GABA levels and attentional blink magnitude was found, which was unsurprising because OCC is regarded as not being principally involved in this attentional blink task (Marois et al., 2004). Instead, smaller blink magnitude (better performance) was found to be associated with higher baseline GABA levels in PFC, but lower baseline GABA levels in PPC (Kihara et al., 2016). The better accuracy for the first target was also associated with higher baseline PFC GABA levels, but not PPC GABA levels. Based on these findings, it was inferred that GABA levels in the PFC and PPC play different roles in visual selective ability and against temporal masking, with an important role assigned to PPC inhibitory function in attentional blink (Corbetta et al., 2008) and to PFC inhibitory

function with respect to general target detection. The inconsistent roles of GABA against visual masking may originate from differences in spatial distraction features (Sumner et al., 2010) and temporal distraction features (Kihara et al., 2016). Apparently, a more refined interpretation about the role of GABA in relation to performance appears warranted when the functional role of a particular brain area in task performance is taken into account.

Besides visual masking, the volitional control in bistable perception and hearing loss under interference induced by noise also requires the ability to suppress task-irrelevant stimuli and concentrate on the task goal. Specifically, Kondo and Kochiyama (2018) investigated the associations between neuro-metabolite levels and volitional control in bistable (visual and auditory) perception. The measure of volitional control was inferred from the perception duration when participants tried only to perceive a specific state and suppress the other. Their findings suggested that higher GABA levels in the primary auditory cortex were associated with better volitional auditory control. In addition, a higher PPC GABA/Glx ratio was associated with better volitional visual and audio control (Kondo et al., 2018). Finally, from the perspective of the auditory modality, evidence from aging populations showed that the more significant speech-in-noise loss was associated with lower GABA levels in the right auditory cortex but not the left one (Dobri and Ross, 2021). This suggested a beneficial role of higher GABA levels in the primary auditory cortex in hearing loss under noise interference. Here, the speech-in-noise loss was identified by the difference between the signal-to-noise ratio when participants can understand 50% of the words and the averaged normative value (Killion et al., 2004).

As discussed above, several studies investigating selective attention support the *GABA interference-suppression hypothesis*, in which higher GABA levels in specific task-related brain areas are associated with better perceptual interference suppression (Dobri and Ross, 2021; Kondo and Kochiyama, 2018; Kondo et al., 2018; Sumner et al., 2010). Presumably, the stronger inhibitory activity associated with higher GABA levels may assist in prioritizing targeted information while minimizing the effects of irrelevant perceptual distractors, leading to better performance. Of note, evidence for the opposite association between GABA levels and interference resolution also exists (Kihara et al., 2016). Furthermore, it is still controversial whether the human capacity to deploy attention and suppress task-irrelevant stimuli is reflected in GABA levels in the sensory cortex, higher cognitive brain areas, or both.

3.2. Associations between baseline GABA levels and motor performance

Motor performance is often characterized through measures of speed (e.g., reaction time) and accuracy. The relationship between baseline SM1 GABA levels and manual motor performance has been examined using both unimanual and bimanual tasks. Stagg et al. (2011a) found an association between faster average reaction times of visually-cued unimanual sequential finger tapping and lower GABA levels in the left SM1 at rest while no association was observed for Glu. Moreover, it was regionally specific as it was not found for OCC GABA levels (Stagg et al., 2011a). Greenhouse and coworkers investigated a bimanual delayed response task consisting of preparatory and imperative periods to study the association among corticospinal excitability, motor reaction times and baseline SM1 GABA levels using both TMS and MRS. In the preparatory period, participants were visually cued about whether the left or right index finger was required to move during the subsequent imperative period in which they were required to respond as fast as possible when a visual signal appeared. Baseline GABA levels in SM1, lateral prefrontal cortex, premotor cortex and OCC were measured. They found that higher resting-state corticospinal excitability was associated with higher GABA levels in SM1 while no associations between reaction times and GABA levels in these four brain areas were reported (Greenhouse et al., 2017).

From the perspective of motor performance accuracy, Chalavi et al. (2018) used a bimanual visuomotor tracking task (BTT; Sisti et al., 2011) to evaluate bimanual coordination performance and learning in young and older adults. Participants made rotational movements with both hands to track a target cursor on the screen. They showed that lower baseline SM1, but not OCC, GABA levels were associated with higher accuracy of bimanual coordination during initial exposure to the task, but this was no longer the case at the more advanced performance levels (Chalavi et al., 2018). These results inspired two tentative hypotheses as potential explanations for the observed behavior-GABA association. First, lower SM1 GABA levels may have induced less inhibition in SM1 and this may have facilitated interhemispheric communication and better bimanual coordination during initial practice. Second, lower SM1 GABA may predispose more performance variation, which may have evoked a richer exploration of performance strategies during initial practice.

In addition to experimental motor paradigms, standardized clinical assessments evaluating manual dexterity and gross-motor function have also been associated with SM1 GABA level. In a combined group of young and older adults, higher SM1 GABA levels were found to be associated with better sensorimotor performance, as assessed by a battery of tasks including the 9-hole pegboard, 2-min walk endurance and some vibrotactile threshold tasks. This association was also observed in the older group alone but not in the young group (Cassady et al., 2019), leading to speculations of an age effect on the GABA-behavior association. Such age effects have also been observed by Maes et al. (2021). They reported that higher overall GABA levels (combined for motor network areas and DLPFC) are associated with better manual dexterity, as assessed by the Purdue Pegboard test, in older adults but worse bimanual tracking performance in young adults.

Even though there is a significant discrepancy in study designs, the preliminary converging picture is that baseline SM1 GABA levels are associated with performance on different types of motor tasks, with regards to reaction speed or accuracy in coordination. Specifically, in young adults, lower SM1 GABA levels seem to correlate with a faster unimanual motor response (Stagg et al., 2011a) and higher accuracy in initial (exploratory) bimanual motor performance in which response speed is not critical (Chalavi et al., 2018). This preliminary evidence may suggest that lower inhibition in the primary motor cortex may lead to faster neural processing speed and greater flexibility in initial movement exploration. We coin this tentatively as the ***GABA-flexibility hypothesis*** that predisposes reduced constraints on behavior. However, this account does not seem to apply to other results in which higher GABA (in SM1) was associated with better motor task performance, (Cassady et al., 2019) and higher GABA (across motor network + DLPFC) with better manual dexterity (Maes et al., 2021), at least in older adults. Thus, the GABA-behavior association may differ between young and older adults as higher overall GABA levels seem to show positive associations with performance in older adults while positive as well as negative associations have been observed in young adults (Maes et al., 2021). Overall, the evidence on the predictive value of baseline GABA in different brain regions for motor performance appears somewhat premature. Furthermore, the question emerges from which brain areas in a given task-relevant network should the GABA levels be extracted to optimally predict motor behavior. Stated more broadly, to what extent is brain regional-specificity and associated function decisive in discovering associations between brain neurochemicals and behavior. This prompts questions about the specific functions associated with the many brain areas that are often involved in various types of tasks.

3.3. Associations between baseline GABA levels and cognitive functioning

Various domains of cognitive behavior have been studied in the context of MRS research, including different types of executive functions and reinforcement or associative learning. Multiple brain regions have been associated with selected subdomains of cognition, including the hippocampus, insula, thalamus, striatum, OCC, prefrontal, parietal, temporal and cingulate cortex. Of specific interest has been the

association between cognitive functioning and GABA in relation to general cognitive decline among the aging population.

3.3.1. General cognitive ability

General cognitive abilities decline with aging, but the degree of decline varies substantially among tasks and individuals. An emerging hypothesis is that maintaining overall cognitive ability in older adults partly depends on neurochemical composition in general and GABA availability in specific brain areas. General cognitive function, as assessed by the Montreal Cognitive Assessment (MoCA) battery (Nasreddine et al., 2005), correlates with higher baseline MRS-measured GABA levels in the midline frontal but not posterior lobe. This association was significant for both the uncorrected GABA levels as well as the CSF-corrected GABA levels (Porges et al., 2017). These findings suggest a regional specificity of GABA levels in their association with cognitive function whereby frontal GABA levels may be predictive for general cognitive ability in the aging population. Additionally, associations have also been observed between higher OCC GABA levels and overall better performance in a compound measure derived from a battery of perception, executive function, and memory tests. This effect was more pronounced in older as compared to young participants (Simmonite et al., 2019). However, it is noteworthy that this study used Cr as the reference metabolite and did not report whether the OCC GABA-behavior association would remain significant after considering tissue composition. These findings may imply that maintaining higher GABA levels in the cognition-related prefrontal areas and other sensory processing brain areas may help slow down the decline of cognitive function with aging. Moreover, even in healthy young adults, associations have been observed between higher OCC GABA levels and lower scores in the cognitive failures questionnaire, which assesses for example memory and distractibility (Sandberg et al., 2014). It would be interesting to find out whether the beneficial effect of higher GABA levels in general cognitive performance may possibly be attributed to more selective neural representations and/or interference control, eventually supporting the *GABA-distinctiveness* or *GABA-interference suppression hypothesis*.

3.3.2. Executive functions

Executive functions refer to a series of high-level cognitive control abilities necessary for goal achievement, such as working memory (updating), response inhibition, selection among competing options and task switching. Generally, better executive functions are accompanied by lower risk of interference through external distractions or internal intrusions. While executive functions may partly share common brain networks, they also have their unique functional requirements (such as the sensory modality of the stimuli used). So far, prominently targeted brain areas in the MRS studies of executive function have been the prefrontal cortex (mainly DLPFC) and anterior cingulate cortex (ACC).

As also observed in other domains, overall executive functions have been shown to decline with aging (Salthouse, 2012). For example, Marenco and colleagues used the Wisconsin Card Sorting Test (WCST; Heaton et al., 1993) as a clinical tool to assess executive functions in relation to GABA levels in dorsal ACC (dACC) (Marenco et al., 2018). While they found a strong age effect for overall performance on the WCST (worse performance with increasing age), no such age effects were detected for general cognitive ability (e.g., visual memory, verbal memory, processing speed and digit span). Moreover, their results showed that higher GABA levels in the dorsal ACC, but not in a white matter control region, were predictive of better performance on WCST in aging adults. These observations suggest that maintaining general executive function in the aging population is associated with higher GABA levels in relevant cognitive processing areas, such as dACC. In view of these results, the beneficial behavioral effect of higher GABA levels might be explained in part by more successful suppression of distractions such that participants can entirely focus on ongoing tasks. However, the relevance of GABA levels in brain areas supporting cognition has also been reported for specific domains of executive functions, such as working memory performance, response inhibition, verbal fluency in language processing and selection as well as decision making, as discussed below.

3.3.2.1. Working memory. Working memory refers to the ability to store information temporarily and to process this information to perform complex cognitive tasks (Baddeley, 1992, 2007). It underlies success in various types of cognitive processes as required for goal achievement. An established experimental paradigm to assess working memory is the 'N-back task' requiring participants to give feedback about the congruency of a currently displayed stimulus (e.g., a letter) with a stimulus presented previously at a specific position (the Nth position) backward in a sequence of stimuli (Kirchner, 1958). The further back this position is located within this stimulus train, the more items need to be held and updated in memory while irrelevant items need to be suppressed; hence, the more difficult the task is. Alternatively, working memory has also been assessed with a subscale of the Wechsler Adult Intelligence Scale (WAIS) (Drozdick et al., 2018), which requires a sequence of numbers to be repeated as heard, in reverse or ascending order. Participants can also observe and repeat a sequence of key taps (soliciting the visual-spatial modality) (Kessels et al., 2000). The theoretical concept underlying these tests suggests that visual and phonological loop processes are directed by an executive component. Recently this classic model was reviewed to incorporate an intermediate episodic buffer that integrates different sensorial modalities (Baddeley and Hitch, 2019). Consequently, in addition to ACC and DLPFC as commonly recognized brain regions involved in working memory - presumably supporting the executive component - areas involved in sensory processing have also been investigated (such as occipital cortex).

Using the N-back task, Takei et al. (2016) examined the inhibition/excitation balance and found that a higher baseline GABA/Glx ratio in both OCC and perigenual ACC (but not mid ACC) voxels was significantly associated with lower memory accuracy when workload increased from the 0-back to 2-back condition. In support of these results, Marsman et al. (2017) found that a higher GABA/Glu ratio (neither GABA nor Glu alone) in the prefrontal cortex was related to a lower working memory capacity, as assessed with the working memory index of the WAIS. Conversely, for OCC, a higher GABA/Glu ratio (driven by relatively lower Glu levels) was associated with higher working memory capacity (Marsman et al., 2017). Partially consistent with these findings, lower working memory capacity, as assessed by a visual-spatial version of the working memory task (Kessels et al., 2000) was associated with lower GABA/Glu ratio (driven by relatively lower GABA levels) in the inferior occipital gyrus (IOG) (Cohen Kadosh et al., 2015). However, no significant associations were observed with neuro-metabolite levels in IFG and intraparietal sulcus. These results indicate that associations between inhibitory/excitatory balance and working memory capacity may depend on the brain area of interest. To further examine the role of DLPFC GABA levels during the different phases of working memory (encoding, maintenance, and recognition), Yoon and coworkers used a working memory paradigm composed of 3 steps: face cue presentation, delay period and final face probe matching. Here, the participants were required to keep the face cue in mind during the delayed time and manage to probe the face in the final step. The difficulty level in the memory load was manipulated by changing 1 or 2 face cues in the first step. Their results revealed that higher DLPFC GABA levels were associated with the smaller magnitude of performance decline when memory load increased. These findings suggest a beneficial effect of higher individual DLPFC GABA levels as the memory load increases and the task becomes more challenging (Yoon et al., 2016). Importantly, this correlation was not observed for GABA levels in OCC serving as control brain region, which further supports the notion that the predictive value of GABA levels is specific to the brain area under investigation and its functional assignment.

In summary, we may witness a somewhat dissociated role of GABA levels in the higher-order processing areas (such as ACC and DLPFC) and the primary sensory areas (such as occipital cortex) across the variety of neuro-metabolite expressions, including GABA/Glx, GABA/Glu and Glu/GABA ratios. Specifically, higher GABA levels in the non-sensory brain areas appear to diminish memory accuracy, leading to worse performance on working memory tasks in younger samples (Marsman et al., 2017; Takei et al., 2016). Based on the available results, we tentatively propose a working hypothesis of excessive GABA-induced inhibition in the prefrontal cortex and ACC, which potentially reduces the cognitive flexibility required for updating temporarily stored information in the brain. The inconsistency in findings (Yoon et al., 2016) may be suggestive of the relevance of the nature of stimuli used for updating memory, which potentially requires additional cognitive control functions, such as flexibility, feature-distinction, or interference-suppression. Inconsistency is also evident in the sensory processing regions: while higher GABA levels in the sensory areas, such as OCC, may boost working memory performance in a simplified task context by protecting against internal interference effects (Cohen Kadosh et al., 2015; Marsman et al., 2017), contrasting evidence has been shown by Takei et al. (2016). Thus, there appears only partial support for either the *GABA-flexibility* or *GABA-interference suppression hypotheses*. Therefore, it remains to be investigated whether higher cognitive flexibility in the prefrontal regions, induced by lower GABA, and higher GABA-induced interference suppression in perceptual areas may be critical for performance success on various types of working memory tasks. This divergence in results may not be too surprising in view of the diversity in working memory tasks across studies requiring either stabilization/shielding of working memory representations and/or flexible updating of working memory based on incoming stimuli.

3.3.2.2. Response inhibition. Response inhibition refers to the suppression of prepotent (unwanted) responses and adherence to the goal-driven response. Response inhibitory control is commonly assessed with tasks requiring the abortion of an intended response, such as a Go/No-go task (Georgiou and Essau, 2011). The subthalamic nucleus (STN), (pre-)supplementary motor area (pre-SMA), right IFG and ACC have been proposed as target regions to facilitate inhibitory control (Aron and Poldrack, 2006; Coxon et al., 2016, 2012; Pornpattananangkul et al., 2016; Weerasekera et al., 2020). Besides the key brain areas known for inhibitory control, other areas, including the striatum, the STG, DLPFC and the hippocampus have also been studied.

Quetscher et al. (2015) used the standard visual Go/No-go task and found that higher striatal GABA levels at baseline conferred a better response inhibition ability while no correlation was found between reaction times in the Go condition and averaged striatal GABA levels (Quetscher et al., 2015). Silveri et al. (2013) also tested the standard Go/No-go task in a group of adolescents and young adults and found higher accuracy in response inhibition being associated with higher ACC GABA levels. Along the same line, using the auditory Go/No-go task, Cheng et al. (2017) found that a higher accuracy rate in the No-go condition was associated with higher baseline GABA levels in the right, but not the left, STG, a region important in auditory signal processing. Alternatively, Koizumi et al. (2018) found that lower DLPFC Glx/GABA ratios (not mentioned whether Glx or GABA drives it) were associated with better inhibitory control (i.e., lower error rate over No-go cues). Conversely, inhibitory responses were not associated with ACC and SMA Glx/GABA ratio. In young and older participants, Hermans and coworkers (Hermans et al., 2018) used a Stop-Signal Task, which requires to stop a prepotent motor response (reactive inhibition) (Logan et al., 2014). Their findings revealed that older adults with higher GABA levels in the pre-SMA exhibited shorter stop-signal reaction times, indicative of better reactive inhibition, while this association was not observed in the young adults or with other brain areas (Hermans et al., 2018).

Besides the classic Go/No-go task, inhibition has also been evaluated in the context of the suppression of unwanted thoughts with a paradigm called the Think/No-Think task (Schmitz et al., 2017), in which participants were required to recall (Think practice) or suppress (No-think practice) previously learned critical cue-word pairs. Their results indicated that higher baseline GABA levels in the hippocampus, but not in DLPFC or a visual control region (OCC), were associated with more efficient thought suppression and thus better forgetting of unwanted word pairs (Schmitz et al., 2017). In this study, the Stop-Signal Task was also used as a control condition to test the general inhibition of action. Because the authors did not find associations between regional GABA levels and motor response inhibition performance in the Stop-Signal Task, they concluded that higher baseline GABA in the hippocampus enables the fronto-hippocampal pathway to exert inhibitory control specific to the suppression of thoughts.

In summary, accumulating evidence discussed here suggests an association between higher GABA levels in areas constituting the response inhibition network and a better suppression of prepotent actions (Cheng et al., 2017; Hermans et al., 2018; Koizumi et al., 2018; Quetscher et al., 2015) and unwanted thoughts (Schmitz et al., 2017). These findings appear to support the *GABA-interference suppression hypothesis*. Furthermore, in light of these findings, the assumption of higher GABA-mediated inhibition as a potential aid to suppress the activation of the prepotent (unwanted) brain network in favor of the goal-oriented response seems conceivable. Additional brain areas, such as the striatum (Quetscher et al., 2015), DLPFC (Koizumi et al., 2018), STG (Cheng et al., 2017) and hippocampus (Schmitz et al., 2017) may also play a role in inhibition in specific experimental contexts. Therefore, the brain areas mainly responsible for suppressing prepotent behavior may vary specifically with the requirements of the task context. In this regard, striatal GABA levels have been shown an association with response inhibition performance in a Go/No-go task (Quetscher et al., 2015) but not in a Stop-Signal Task (Hermans et al., 2018). Likewise, hippocampal GABA levels were specific to inhibition-induced thought suppression but not general response inhibition, as tested with the Stop-Signal Task (Schmitz et al., 2017).

3.3.2.3. Conflict resolution. Some studies make use of specific task environments that conflict with prepotent response tendencies to investigate conflict resolution ability. A common experimental paradigm employed in this context is the Simon task (Simon and Wolf, 1963) or the Stroop task (Stroop, 1935), which require a response upon a semantically or spatially conflicting cue, e.g. right hand response upon a stimulus provided on the left or through the cue word 'left'. The underlying theoretical concept is that conflict resolution ability is required to overcome established natural responses that are triggered by or aligned with optimal conceptual or spatial stimulus-response compatibility. Under these conflicting circumstances, the more compatible responses are regarded as inducing interference when completing less or incompatible but required task goals. To some extent, the brain networks responsible for conflict resolution may partially overlap with networks responsible for response inhibition as both abilities require inhibition of prepotent (interfering) responses.

Dharmadhikari et al. (2015) used a modified Simon task to test the association between conflict resolution ability and striatal and thalamic GABA levels. Here, the correspondence effect was used to assess the ability against interference, as measured by the reaction time difference when the visual stimulus and the responsive hand appeared on the same side (correspondent condition) versus the opposite sides (non--correspondent condition). Their findings revealed that higher striatal GABA levels were predictive of shorter reaction times across all four conditions (parallel or crossed arms combined with correspondent or non-correspondent condition). However, higher thalamic GABA levels were predictive of lower correspondence effects (i.e., better in overcoming interference). This finding was regarded as reflecting the

different functions of the striatal and thalamic GABAergic system for general speed effects and correspondence effects (against interference), respectively. However, it is worth mentioning that these associations were only observed in combined groups of healthy participants and those with Parkinson's disease, but not in either separate group. We suggest this study to support the *GABA-interference suppression hypothesis* in that higher thalamic GABA levels attenuate the position-induced interference. Consistent with the latter hypothesis, Haag et al. (2015) found that higher striatal GABA levels were associated with higher accuracy in the most challenging Simon task condition (cross-hand and non-correspondent) in a sample of airplane pilot trainees and non-trainees.

3.3.2.4. Semantic selection and decision making. Selecting one option among multiple competing alternatives and decision-making are abilities that require people to suppress irrelevant information and prioritize the most appropriate choice. Again, the underlying theoretical construct is that inhibitory function plays an important role in shaping these cognitive abilities. This behavioral capacity is frequently assessed with priming tests like the semantic completion or semantic association tasks (Hutchison et al., 2013; Neely, 1991), which require the filtering and selection of appropriate words among multiple options to complete a sentence or make an association for a given context. Baseline GABA levels in the prefrontal cortex, a crucial region for selection, as well as in the anterior temporal lobe (ATL), a crucial region for semantic processing, have been studied in memory retrieval and decision making. Higher baseline GABA/Glx ratio (but not GABA or Glx alone) in the lateral prefrontal cortex was shown to be associated with faster selection speed in a sentence completion task (de la Vega et al., 2014). These findings were interpreted as an indicator for stronger inhibition induced by GABA in the prefrontal cortex to boost the efficiency of goal-oriented decision-making required in semantic processing. In addition, in a semantic association task, requiring to select one of two optional pictures, a positive link was found between better semantic association performance and higher GABA concentration in the ATL (Jung et al., 2017). These findings support the hypothesis that, in order to make an appropriate choice, suppression of the competing semantic representations is needed. In summary, when choosing between competing semantic representations is required, higher GABA appears beneficial for selection performance. If this may be achieved through GABA-induced inhibition of nonrelevant semantic representations, it supports the *GABA-interference suppression hypothesis*.

3.3.2.5. Verbal fluency and language integration. Verbal fluency tests are often used to evaluate executive function and serve as a screening for cognitive decline. This ability can be assessed using the phonemic (or letter) fluency task (Hughes, 1970) and the semantic (or category) fluency task (Benton, 1968). In phonological processing, as assessed by the letter fluency task, participants are required to report within one minute as many nouns as possible that start with a specific letter. In a semantic fluency task, participants are required to report nouns belonging to a specific category, such as listing as many animals as possible within one minute. In both tasks, the number of correct words is measured as behavioral performance level. Obviously, there is an evident language component apart from the executive functions tapped in these tasks. This suggests several candidate regions for GABA level assessment.

In this research domain however, the association between GABA levels in key brain areas and performance is not yet clear. Nakai and coworkers did not find a correlation between GABA levels in left or right IFG and letter fluency (Nakai and Okanoya, 2016). In another comparable study, neither the GABA levels in the ACC nor in the posterior cingulate cortex (PCC) were related to letter fluency performance in a combined group of healthy subjects and subjects with mild cognitive impairment (Oeltzschner et al., 2019). For the semantic category fluency task, however, better performance was associated with lower GABA levels in the left IFG (Nakai and Okanoya, 2016). The different results obtained in these two tasks may be due to the fact that semantic processing requires a much higher cognitive load and more associated memory retrieval than phonological processing. Because the latter study suggested an important role of vocabulary size in the letter fluency task and an important role of lexical access speed in the category fluency task (Shao et al., 2014), the category fluency task may be more sensitive to individual differences in executive function. In the context of semantic processing, less inhibition in IFG induced by lower baseline GABA levels may pave the way for more uninhibited prolific retrieval of associative memories. This appears to be consistent with the *GABA-flexibility hypothesis* but more research is clearly required.

The integration of written and spoken language is critical for developing children's reading ability. Del Tufo et al. (2018) investigated the associations between baseline OCC GABA levels and children's audio-visual integration ability. Here, in each trial, children heard an audio stimulus and were then required to choose the matched visual stimuli from two alternatives as fast as possible. Reaction times were used to represent the cross-modal language integration ability. Their evidence showed that lower OCC GABA levels were associated with faster response, which indicated that reduced inhibition in OCC may have enhanced or facilitated the cross-modal language integration. We tentatively suggest this to be consistent with the *GABA-flexibility hypothesis*.

3.3.3. Probabilistic and associative learning

The ability to differentiate stimuli and link them with environmental contingencies is essential for adaptation in everyday life. Bezalel et al. (2019) used a reinforcement learning paradigm, in which participants faced a two-alternative forced-choice task corresponding to a systematically varying likelihood of monetary loss or gain: (a) uncertainty condition with high cognitive load (50/50), (b) discrimination learning condition with lower cognitive load (80/20), and (c) a control condition (00/00). Participants learned the associations between the auditory input and the probability of monetary loss/gain in the discrimination condition while not showing a preference in the other conditions. Higher baseline GABA levels in dACC, a crucial region for error- and reward-guided decision making, were found to correlate with a higher probability of choosing the option with high monetary gain in discrimination learning. The distinctive role of higher dACC GABA levels may be important in this task as it requires discriminating the gaining probability accompanied with the appropriate sensory inputs. As such, we interpret the results as support for the *GABA-distinctiveness hypothesis*.

In order to investigate the association between dACC GABA and probabilistic learning, Scholl et al. (2017) used a multi-dimensional reinforcement learning paradigm, in which participants repeatedly chose between the same two options trying to maximize the rewards and minimize the efforts required along with their options. The ability to use the learned reward-effort model to guide their choices, rather than just relying on the shown probability, was measured as a learning result. The authors found that both higher Glx and lower GABA levels in dACC were independently associated with better learning results. In contrast to the results of Bezalel and colleagues, the negative GABA-performance association found by Scholl and coworkers appears inconsistent with the *GABA-distinctiveness hypothesis* and may to some extent be explainable by the lower complexity and cognitive load required in the latter tasks.

Spurny et al. (2020) investigated the relevance of bilateral hippocampal, thalamic, and insular GABA for associative learning. They employed a paradigm in which the association of pairs of faces had to be learned daily over 3 consecutive weeks. This study uncovered a 'regionally selective' correlation between higher resting hippocampal GABA levels and better initial retrieval performance because no correlation with retrieval performance was found for insular or thalamic GABA levels and Glx levels. GABA's role in successful retrieval of the

paired facial information may be mediated by suppressing the interference induced by irrelevant facial pairs. We therefore propose that being able to suppress irrelevant information (being associated with higher GABA in the hippocampus) may play an important role in the associative learning result. Accordingly, we interpret these results as being consistent with the *GABA-interference suppression hypothesis*.

4. General summary

This review summarizes and converges upon the associations between MRS-assessed baseline GABA levels in specific brain areas (Fig. 1) and three important generic behavioral functions, leading to emerging preliminary hypotheses about the potential role of GABA in behavior (Fig. 2). It is important to underscore that substantial experimental work will be required to further confirm or refute these hypotheses.

Firstly, the *GABA-distinctiveness hypothesis* states that maintaining appropriate neural suppression in (perceptual) processing regions via 'higher' baseline GABA levels is associated with more distinctive representations, leading to higher perceptual sensitivity, discrimination and acuity (Fig. 2). Converging evidence from different task domains supports this hypothesis and this is linked with the establishment of distinct sensory representations in the primary perceptual processing areas (Section 3.1.1). Furthermore, preliminary evidence shows that cognitive learning tasks, requiring distinctiveness of probabilities, are linked to higher GABA levels in brain areas supporting cognition (Section 3.3.3). Accordingly, this GABA-behavior association may not necessarily be restricted to perceptual processing areas.

Secondly, the *GABA-interference suppression hypothesis* argues that 'higher' GABA levels in task-related brain areas may help protect against interference induced by irrelevant stimuli or prepotent responses, thereby leading to superior performance (Fig. 2). GABA levels in the brain inhibition network (as part of executive functions) are associated with more optimal goal-oriented performance that requires abandoning prioritized or preferred motor or mental responses or better suppression of prepotent responses (Section 3.3.2). Consequently, this role of GABA points to keeping behavior in check against the background of distractions and this is often associated with the deployment of attention. Similarly, better suppression of perceptual or cognitive distractions or prepotent perceptual representations may go along with higher GABA levels. The majority of studies looking into perceptual illusions, selective attention for perceptual stimuli (Section 3.1.2) and conflict resolution (Section 3.3.2) suggest an important role for higher GABA levels in filtering out interference. This is associated with strong goal maintenance and implementation.

Thirdly, the *GABA-flexibility hypothesis* posits that 'lower' baseline GABA levels may contribute to performance requiring flexible retrieval of information or behaviors (Fig. 2). This hypothesis is supported in tasks requiring motor efficiency (motor response speed and accuracy) or cognitive flexibility (working memory updating, verbal fluency and language integration). Specifically, lower baseline SM1 GABA levels correlate with faster motor responses and higher accuracy of motor behavior during initial task exposure (Section 3.2). Similarly, in the cognitive domain, higher cortical excitability induced by lower baseline frontal GABA levels correlates with better performance in cognitive flexibility, such as in tasks assessing verbal fluency (Section 3.3.2). We assume that less inhibitory tone, associated with lower GABA levels, reduces the break on neural activity and predisposes abundance and flexibility in thoughts and actions.

These hypotheses may not be mutually exclusive yet are distinguishable to some extent. For example, neural distinctiveness of representations may require some degree of suppression of non-relevant physical properties or filtering out distractors in order to construct such representations. Behavioral flexibility may be associated with increased distractibility. More research is certainly required to validate the relationships between behavior and GABAergic activity in order to refine the neurophysiological foundations of these associations. It turns out that, depending on the tasks under investigation and the underlying cognitive processes they capture, both lower as well as higher GABA levels may be beneficial for performance, at least in young adults. To that extent, GABA may mediate the potential trade off between stability and flexibility as two extremes on a cognitive control continuum. On the one hand, cognitive stability may promote persistence and perseverative behavior shielded from interference but also reduced adaptation to changing contexts or novel stimuli (high GABA tone). On the other hand, cognitive flexibility may imply less constrained and more exploratory behavior which may also be more distractible, yet more appropriate for set shifting (low GABA tone). With respect to the aforementioned three hypotheses, the following qualifications should be considered.

First, although the synthesized results underscore a vital role of GABA levels in various expressions of human performance, conflicting findings have also been reported and it is currently difficult to account for these. Distinct functions and their associated locus of regional activity in the brain may be one factor contributing to this divergence besides methodological features, including differences in task paradigms, neurochemical detection techniques and underpowered studies suffering from reproducibility problems.

Second, it appears that research so far has primarily been focused on the primary sensory cortices (visual, auditory, somatosensory), primary sensorimotor cortex (SM1) and some generic prefrontal cognitive processing areas (such as DLPFC and ACC). This makes sense because accumulating evidence suggests a function-related region-specific role of GABA. However, from a broader perspective, whether this GABA-behavior association only applies to the most critically involved primary brain areas that directly support behavior or whether this extends

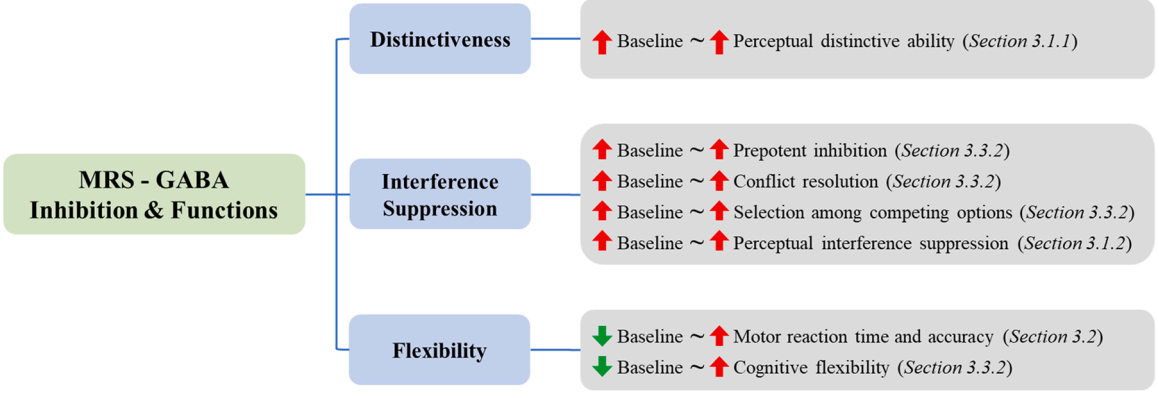

Fig. 2. The functions of baseline MRS-GABA in behavior. The red upward arrow represents bigger and larger. The green downward arrow represents lower. The tilde (~) represents associations.

to secondary-assistive brain areas remains to be further explored. This also pertains to the possible contribution of subcortical or below-cortical areas that have been vastly understudied. From a technical standpoint, this begs for a transition from single-voxel to multi-voxel MRS approaches that target a broader cortico-subcortical territory.

Third, we observed that the association between MRS-assessed GABA levels and behavioral performance varies across different task domains in young adults; i.e., for some tasks, higher GABA levels are associated with better performance, and for others, with worse performance. To the extent that resting GABA levels can be considered relatively stable (GABA tone) (Evans et al., 2010; Greenhouse et al., 2016; Near et al., 2014; Wijtenburg et al., 2013), this may be reflective of an individual's relative positioning on the continuum ranging from high stability to high flexibility. However, research in older adults appears to show that preserving sufficiently high GABA levels in task-related brain areas is invariably predictive of better performance, regardless of task domain (Hermans et al., 2018; Maes et al., 2021; Porges et al., 2017; Simmonite et al., 2019). Further confirmation across a broader range of cognitive and motor tasks as well as across the larger cortical or subcortical territory is mandatory to confirm and unravel this peculiar age effect. One of the potential mechanisms underlying this effect may refer to age-related decreases in GABA levels and other neurochemicals (Chalavi et al., 2018; Cuypers et al., 2021; Hermans et al., 2018; Marenco et al., 2018; Porges et al., 2021; Porges et al., 2017). Perhaps a critical threshold in GABA availability and the associated reduction of general inhibitory capacity in older adults is a critical factor mediating this effect.

Fourth, we have primarily restricted our review to the study of baseline GABA levels without considering the potential role of modulation of neuro-metabolites as a result of brain stimulation, repeated practice or learning. This modulatory capacity may prove to be critical for understanding neuroplastic processes involved in shaping new behavior. Nevertheless, the modulation range may be contingent upon the level of GABA that is available during the resting state. Although we mentioned good stability of MRS-assessed GABA over short and long time epochs (Evans et al., 2010; Greenhouse et al., 2016; Near et al., 2014; Wijtenburg et al., 2013), GABA levels have been reported to vary at least with the menstrual cycle in females (Harada et al., 2011; Liu et al., 2015). More broadly, we need to better understand how stable GABA levels are during the resting state but also how responsive these are during involvement in a task or as a result of brain stimulation. This refers to the tonic and phasic features of GABA levels in individuals.

In summary, we hope that the identification of these three potentially powerful functions associated with GABA level will inspire future research endeavors in different behavioral domains via hypothesis-driven approaches. This may ultimately lead to an expansion of the different roles GABA may play in behavior.

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Conflict of interest

The authors have no conflicts of interest to declare.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.pneurobio.2022.102247.

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