REVIEW

Motor inhibition efficiency in healthy aging: the role of γ-aminobutyric acid

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Abstract

The ability to cancel a motor response is critical for optimal functioning in various facets of daily life. Hence, efficient inhibitory motor control is a key function throughout the lifespan. Considering the fact that inhibitory motor function gradually declines with advancing age, it is not surprising that the study of motor inhibition in this age group is gaining considerable interest. In general, we can distinguish between two prominent types of motor inhibition, namely proactive and reactive inhibition. Whereas the anticipation for upcoming stops (proactive inhibition) appears readily preserved at older age, the ability to stop an already planned or initiated action (reactive inhibition) generally declines with advancing age. The differential impact of aging on proactive and reactive inhibition at the behavioral level prompts questions about the neural architecture underlying both types of inhibitory motor control. Here we will not only highlight the underlying structural brain properties of proactive and reactive inhibitory control but we will also discuss recent developments in brain-behavioral approaches, namely the registration of neurochemical compounds using magnetic resonance spectroscopy. This technique allows for the direct detection of the primary inhibitory neurotransmitter in the brain, *i.e.*, γ-aminobutyric acid, across the broader cortical/subcortical territory, thereby opening new perspectives for better understanding the neural mechanisms mediating efficient inhibitory control in the context of healthy aging. Ultimately, these insights may contribute to the development of interventions specifically designed to counteract age-related declines in motor inhibition.

Key Words: *proactive inhibition; reactive inhibition; motor inhibition; healthy aging; gamma-aminobutyric acid; magnetic resonance spectroscopy; GABA; inhibitory neurotransmitter; neuroimaging*

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Complex behavior does not only require excitation of dedicated brain areas but also recruitment of inhibitory networks to tune behavior according to environmental contingencies. The ability to inhibit inappropriate behavior plays a key role in our daily lives and its importance cuts across multiple domains such as emotional, cognitive and motor behavior. Undoubtedly, inhibitory control enables high levels of flexibility and adaptability in many real-world situations. For example, a lack of inhibition can be disruptive for social interactions; just imagine yourself insulting a driver who almost hurt you when crossing the road or hitting someone at the peak of anger during a heated discussion. Also in the motor context, preventing or suppressing an already planned or initiated motor response plays a key role in daily circumstances and even has survival value. For example, aborting to cross the street when suddenly detecting a fast approaching car can be a life threatening condition. Overall, this exemplifies the critical role of a healthy balance between processes of excitation and inhibition in the brain. There are many techniques to study inhibition. Here we approach the study of human age-related alterations in inhibitory processes *via* the registration of neurochemical compounds using medical imaging technology. Our work reveals that levels of gamma-aminobutyric acid (GABA) - the chief inhibitory neurotransmitter in the human brain - is altered during healthy aging and impacts the quality of inhibitory control in older adults (Levin et al., 2014; Hermans et al., 2018). We have performed a PubMed literature search of articles published in the period January 2016–November 2018 on the neural underpinnings of proactive and reactive inhibitory motor control in healthy aging.

The study of inhibitory processes has a long history in experimental psychology. Inhibitory control is considered to be one of the distinct processes that belongs to executive functions, known to be critically important for the control of action. We can distinguish between at least two prominent types of inhibitory motor control, namely reactive and proactive inhibition. Reactive inhibition is the abrupt stopping of an already planned or initiated action. It is triggered by an unexpected stop signal such as a car that suddenly approaches you from the side. Conversely, proactive inhibition may come into play when the upcoming stop process can be anticipated as a result of environmental factors, such as driving more slowly in close proximity

to a primary school. The increased expectation of children crossing the street leads us to drive much more cautiously.

The study of inhibitory control or a lack thereof also has clinical relevance. Addiction to food, alcohol, drugs, *etc*. is a major burden with tremendous consequences for the individual as well as society. Some pathological conditions are also associated with general inhibitory control deficits (*e.g*., tourette syndrome and attention-deficit/hyperactivity disorder). But inhibitory control is also modulated across the lifespan. It is gradually shaped during adolescence when risky behavior is prominent and not yet fully under control. At higher age, inhibitory function is compromised and may provide an important clue into processes of 'brain dedifferentiation'. More specifically, the dedifferentiation hypothesis points to increased brain activity (reduced specificity of neural representations) and increased connectivity (or reduced segregation) among the different functional networks in older as compared to young adults (Logan et al., 2002; King et al., 2017).

From the perspective of different modes of inhibitory control, recent literature suggests that older adults are readily able to anticipate upcoming stops (proactive inhibition) and this is shaped by lifelong experience. Conversely, stimulus-driven stopping in response to an external cue (reactive inhibition) gradually deteriorates at higher age (Smittenaar et al., 2015; Bloemendaal et al., 2016; Kleerekooper et al., 2016). Consequently, these behavioral findings suggest distinct neural substrates underlying proactive and reactive inhibition of which the latter might be more susceptible to age-related declines.

To date, a considerable amount of research has been devoted to investigation of the underlying structural brain properties of motor inhibition and their differential involvement in proactive and reactive inhibition. In brief, efficient inhibitory control is known to rely on the integrity of a fronto-basal-ganglia network (Jahanshahi et al., 2015) (**Figure 1**). Basically, the frontal part of this network produces a stop command *via* the basal ganglia in order to intercept the planned motor action that was generated in the primary motor cortex (M1) whenever needed. Two regions of the prefrontal cortex, namely the right inferior frontal cortex and pre-supplementary motor area, are also thought to play a critical role in successful stopping and are thus considered key nodes of the motor inhibition network. At the subcortical level, reactive inhibition is thought to rely primarily on the involvement of subthalamic nucleus (Aron and Poldrack, 2006), whereas proactive inhibition appears to be more dependent on the striatum (Aron, 2011).

In spite of the well-characterised structural scaffold of inhibitory motor control, the neurochemical architecture of the fronto-basal-ganglia network is less well characterized in the context of healthy aging. In general, there is mounting evidence that the GABA system is altered during healthy aging (Levin et al., 2014). More specifically, studies in which use is made of non-invasive brain stimulation techniques have shown that older adults exhibit a reduced capacity to modulate $GABA_A$- and $GABA_B$-ergic inhibition and this is associated with degraded motor performance (Levin et al., 2014). Moreover, evidence from both animal and human studies suggests an age-related decrease in GABA level within various brain regions (Gao et al., 2013).

Recently, we investigated the role of GABA level within the fronto-basal-ganglia network and its age-related consequences for inhibitory motor control. Using magnetic resonance spectroscopy, we quantified baseline GABA level in key nodes of the fronto-basal-ganglia network, that is, the right inferior frontal cortex, pre-supplementary motor area, bilateral striatum and left sensorimotor cortex (Hermans et al., 2018). Magnetic resonance spectroscopy protocols were carried out on a magnetic resonance scanner and allowed for a non-invasive and *in vivo* detection of local GABA levels. Although the concentration of GABA is relatively low and thus less strongly represented as compared to other metabolites in the human brain, we were able to accurately quantify GABA levels within specific brain areas by isolating the GABA signal from the spectrum, using MEGAPRESS (Puts and Edden, 2012). To determine the level of proactive and reactive inhibitory control, both young and older adults performed an anticipated response version of the stop-signal task with varying levels of stop-signal probability (Coxon et al., 2012). More specifically, participants were instructed to lift their right index finger from a switch when a filling bar crossed a predefined target line (go trial). The target line was fixed across trials such that participants could precisely time their responses. In order to estimate the latency of the stop process (*i.e*., stop-signal reaction time), stop trials were included in which the participants had to cancel their already planned action. That is, the bar stopped automatically before crossing the target line such that participants were required to inhibit the movement of lifting their finger from the switch. Using this stop-signal paradigm, we were able to quantify the efficiency of reactive inhibitory control. Furthermore, the stop-signal probability was manipulated in order to assess the degree of proactive response slowing, *i.e*., participants slowed down as a function of whether less or more stops could be anticipated during upcoming trials. At the behavioral level, we demonstrated age-related decrements in reactive inhibitory control whereas proactive inhibition remained intact,

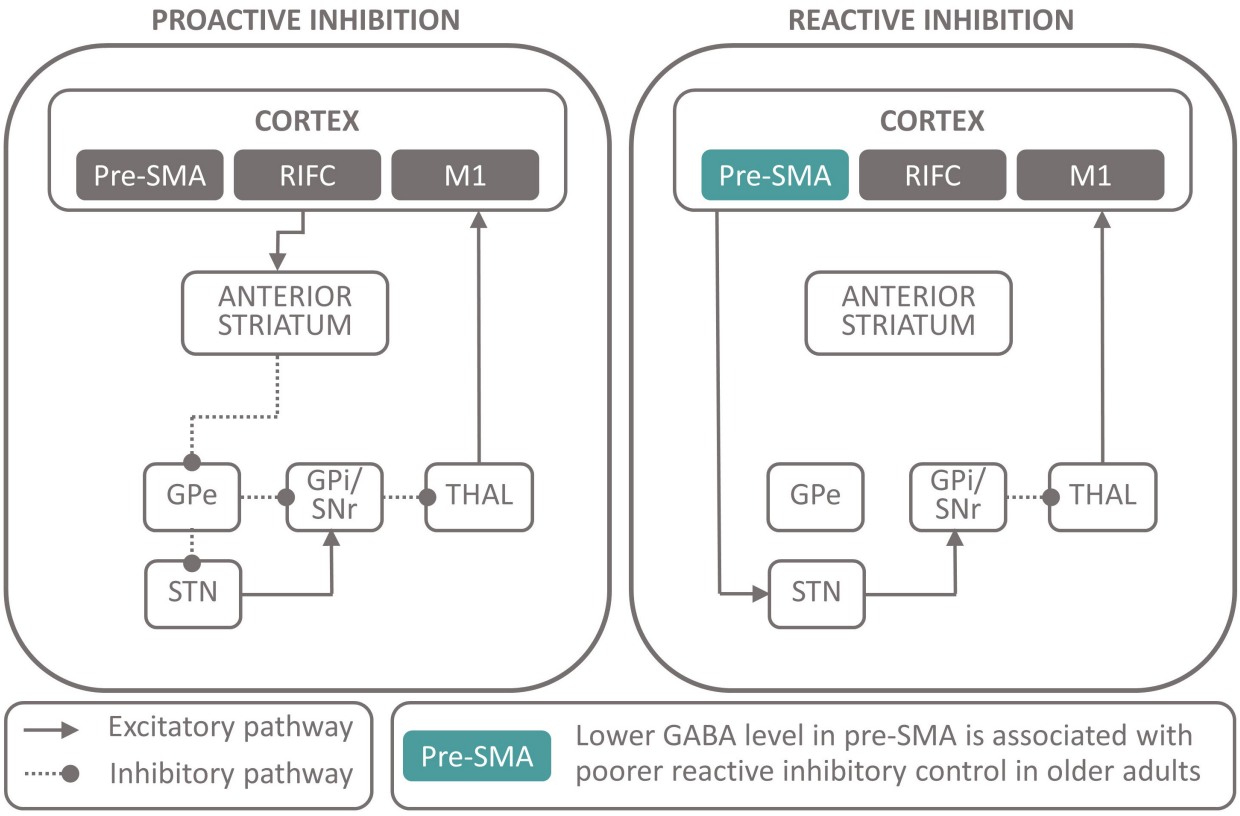

Figure 1 Tentative scheme of the fronto-basal-ganglia pathways proposed to mediate proactive and reactive inhibition.
Our data show that in older adults, GABA levels within the pre-SMA are functionally relevant for reactive inhibitory control. More specifically, lower GABA levels are associated with longer stop-signal reaction times or poorer reactive inhibitory control in older but not in young adults (Hermans et al., 2018). Pre-SMA: Pre-supplementary motor area; RIFC: right inferior frontal cortex; M1: primary motor cortex; STN: subthalamic nucleus; GPe: external segment of the globus pallidus; GPi: internal segment of the globus pallidus; THAL: thalamus; SNr: substantia nigra pars reticulata. Figure 1 is adapted from Leunissen et al. (2016) and Aron (2011).

in agreement with previous literature. With respect to the neurochemical correlates, the magnetic resonance spectroscopy data demonstrated that GABA levels within regions associated with the fronto-basal-ganglia network mediating motor inhibition were found to be lower in older as compared to young adults. Furthermore, we showed that GABA levels were functionally relevant for behavioral performance in older adults. In particular, lower GABA levels in the pre-supplementary motor area were predictive of longer stop-signal reaction times, that is, poorer reactive inhibitory control in older but not young adults (Hermans et al., 2018).

The integrity of the GABA system is of utmost importance for efficient inhibitory control and reactive inhibition in particular. In fact, our data suggests that reactive inhibitory control is an executive function that is vulnerable to degeneration of the aging brain (Coxon et al., 2012; Hermans et al., 2018). Even though age-related declines in GABA level and other neurochemical compounds have been observed, whether and how this is triggered by structural brain changes remains less clear. In this respect, it is less likely that the age-related effects on GABA level are solely driven by brain atrophy (voxel composition). Rather, emerging evidence from animal studies points towards a possible decline in GABA production and/or a degradation in GABAergic inhibitory interneurons (Ling et al., 2005; Hua et al., 2008), although further investigation is required. Interestingly, despite the fact that GABA level was altered across all tested brain regions in the total group of older adults as compared to young adults, reactive inhibition was better preserved in those older adults who maintained higher GABA levels within the pre-supplementary motor area, a key hub of the motor inhibitory network. This would also fit with the observation that patients showing a considerable deterioration in motor inhibition efficiency, such as attention-deficit/hyperactivity disorder and Tourette's syndrome, also demonstrate degraded GABAergic functioning (Puts et al., 2015). Alternatively, the subthalamic nucleus, an important node in the mediation of reactive inhibition, may be particularly susceptible

to age-related degradation as its connections with the cortex are known to be less abundant as compared with those of the striatum (Inase et al., 1999). Indeed, the pathways known to be involved in proactive inhibition are thought to be richer in quantity, and this might possibly account for the finding that proactive inhibition appears still preserved at older age (**Figure 1**).

Altogether, research on the role of GABA within the fronto-basal-ganglia network and its implications for proactive and reactive inhibition sheds light on the underlying neural mechanisms of age-related deficits in motor inhibition efficiency. Nevertheless, even though resting-state (baseline) GABA levels provide a window into the processes mediating motor inhibition, further research examining the role of GABA and its modulatory capacity within the fronto-basal-ganglia network during task execution is warranted (*i.e.*, its task-related dynamics). In view of the demographic evolution of society, with the cohort of older adults being the fastest growing subpopulation, our ultimate aim is to contribute to a basic understanding of neural mechanisms involved in inhibitory control. We argue that the study of inhibitory function is critically important for understanding mechanisms of 'dedifferentiation' in the aging brain and its consequences for brain structure, function, and connectivity. This body of knowledge will be instrumental for the development of interventions or rehabilitation procedures to counteract age-related deterioration in motor functioning in general and motor inhibition in particular. If we want to empower, support and sustain healthy aging, there is an urgent need to characterize age-related alterations to the GABAergic system and its consequences for motor and cognitive deficits.

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References

Aron AR (2011) From reactive to proactive and selective control: developing a richer model for stopping inappropriate responses. Biol Psychiatry 69:e55-68.
Aron AR, Poldrack RA (2006) Cortical and subcortical contributions to Stop signal response inhibition: role of the subthalamic nucleus. J Neurosci 26:2424-2433.
Bloemendaal M, Zandbelt B, Wegman J, van de Rest O, Cools R, Aarts E (2016) Contrasting neural effects of aging on proactive and reactive response inhibition. Neurobiol Aging 46:96-106.
Coxon JP, Van Impe A, Wenderoth N, Swinnen SP (2012) Aging and inhibitory control of action: cortico-subthalamic connection strength predicts stopping performance. J Neurosci 32:8401-8412.
Gao F, Edden RA, Li M, Puts NA, Wang G, Liu C, Zhao B, Wang H, Bai X, Zhao C, Wang X, Barker PB (2013) Edited magnetic resonance spectroscopy detects an age-related decline in brain GABA levels. Neuroimage 78:75-82.
Hermans L, Leunissen I, Pauwels L, Cuypers K, Peeters R, Puts NAJ, Edden RAE, Swinnen SP (2018) Brain GABA Levels are associated with inhibitory control deficits in older adults. J Neurosci 38:7844-7851.
Hua T, Kao C, Sun Q, Li X, Zhou Y (2008) Decreased proportion of GABA neurons accompanies age-related degradation of neuronal function in cat striate cortex. Brain Res Bull 75:119-125.
Inase M, Tokuno H, Nambu A, Akazawa T, Takada M (1999) Corticostriatal and corticosubthalamic input zones from the pre-supplementary motor area in the macaque monkey: comparison with the input zones from the supplementary motor area. Brain Res 833:191-201.
Jahanshahi M, Obeso I, Rothwell JC, Obeso JA (2015) A fronto-striato-subthalamic-pallidal network for goal-directed and habitual inhibition. Nat Rev Neurosci 16:719-732.
King BR, van Ruitenbeek P, Leunissen I, Cuypers K, Heise KF, Santos Monteiro T, Hermans L, Levin O, Albouy G, Mantini D, Swinnen SP (2017) Age-related declines in motor performance are associated with decreased segregation of large-scale resting state brain networks. Cereb Cortex:1-13.
Kleerekooper I, van Rooij SJH, van den Wildenberg WPM, de Leeuw M, Kahn RS, Vink M (2016) The effect of aging on fronto-striatal reactive and proactive inhibitory control. Neuroimage 132:51-58.
Leunissen I, Coxon JP, Swinnen SP (2016) A proactive task set influences how response inhibition is implemented in the basal ganglia. Hum Brain Mapp 37:4706-4717.
Levin O, Fujiyama H, Boisgontier MP, Swinnen SP, Summers JJ (2014) Aging and motor inhibition: a converging perspective provided by brain stimulation and imaging approaches. Neurosci Biobehav Rev 43:100-117.
Ling LL, Hughes LF, Caspary DM (2005) Age-related loss of the GABA synthetic enzyme glutamic acid decarboxylase in rat primary auditory cortex. Neuroscience 132:1103-1113.
Logan JM, Sanders AL, Snyder AZ, Morris JC, Buckner RL (2002) Under-recruitment and nonselective recruitment: Dissociable neural mechanisms associated with aging. Neuron 33:827-840.
Puts NA, Edden RA (2012) In vivo magnetic resonance spectroscopy of GABA: a methodological review. Prog Nucl Magn Reson Spectrosc 60:29-41.
Puts NA, Harris AD, Crocetti D, Nettles C, Singer HS, Tommerdahl M, Edden RA, Mostofsky SH (2015) Reduced GABAergic inhibition and abnormal sensory symptoms in children with Tourette syndrome. J Neurophysiol 114:808-817.
Smittenaar P, Rutledge RB, Zeidman P, Adams RA, Brown H, Lewis G, Dolan RJ (2015) Proactive and reactive response inhibition across the lifespan. PLoS One 10:e0140383.

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