

The Role of Tryptophan and Tyrosine in Executive Function and Reward Processing

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ABSTRACT: The serotonergic precursor tryptophan and the dopaminergic precursor tyrosine have been shown to be important modulators of mood, behaviour and cognition. Specifically, research on the function of tryptophan has characterised this molecule as particularly relevant in the context of pathological disorders such as depression. Moreover, a large body of evidence has now been accumulated to suggest that tryptophan may also be involved in executive function and reward processing. Despite some clear differentiation with tryptophan, the data reviewed in this paper illustrates that tyrosine shares similar functions with tryptophan in the regulation of executive function and reward, and that these processes in turn, rather than acting in isolation, causally influence each other.

KEYWORDS: Tryptophan, serotonin, tyrosine, executive function, reward, reinforcement, cognitive flexibility, dopamine

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Introduction

Serotonin (5-HT) has long been established as an important modulator of mood, particularly with respect to the pathophysiology of depression. A substantial amount of this evidence has come from studies employing the acute tryptophan depletion (ATD) procedure, where 5HT levels are lowered by reducing the availability of its precursor, tryptophan.¹ Despite this well-established role, 5HT has also implicated in the regulation of executive functions, specifically response inhibition and its relation to impulse control^{2–8} (with the dopaminergic system [DA] also having an important involvement).⁹ Additionally, over the last decade several investigations in both animals and humans have implicated 5-HT in reward processing and goal-directed behaviour,^{10–16} domains normally attributed to be under the control of the DA system.¹⁷

The purpose of this review and its related novelty is therefore to bring together research findings in which tryptophan and the dopaminergic precursor tyrosine were manipulated in the context of executive function and reward processing in humans. By comparing and contrasting tryptophan and tyrosine studies, we will be able to isolate the influences that presynaptic manipulations of serotonergic and dopaminergic activity have on these processes.

The evidence reviewed for both tryptophan and tyrosine will come from the following three sources: (1) ATD and acute phenylalanine and tyrosine depletion (APTD) studies (2) tryptophan and tyrosine loading and (3) polymorphisms in genes encoding tryptophan hydroxylase (TPH1 and TPH2). To the best of the author's knowledge, there have been no investigations on the association between genetic polymorphisms in tyrosine hydroxylase (TH) and executive function/reward processing (of note, TH polymorphisms have been linked to bipolar disorders,¹⁸ personality traits,¹⁹ schizophrenia,²⁰ alcohol dependence²¹ and suicide attempts)²² and therefore TH studies will not be reviewed.

This review consists of the following four parts: (a) an evaluation of the literature on the serotonergic and dopaminergic systems (broadly) and their modulation of mood (depression in particular), executive function and reward processing; (b) an overview of the mechanisms of the ATD and APTD procedures (as most of the reviewed evidence relies on the ATD/APTD literature); (c) a summary of the findings which relate to the role of tryptophan and tyrosine in executive function; (d) and reward processing.

PubMed (<https://pubmed.ncbi.nlm.nih.gov>) was used to search for all articles. The publication selection criteria with respect to (c) and (d), consisted of the following: (1) the articles had to be original, peer-reviewed manuscripts, published in English from 1990 to 2020; (2) the studies must have been conducted in healthy volunteers but not in healthy and older individuals; (3) must have used cognitive tasks that measure executive function and reinforcement; (4) the articles were retrieved using the following search terms: 'tryptophan', 'tryptophan depletion', 'tyrosine', 'tyrosine depletion', 'executive', 'reinforcement', 'reward', 'learning', 'TPH1', 'TPH2'. In order to minimize the risk of missing potentially relevant articles, the reference list of every retrieved paper in which the above search terms were used was extensively examined. Studies that failed to meet the above criteria were excluded. A summary of all the reviewed studies for section (c) and (d) has been reported in Tables 1–4.

The serotonergic and dopaminergic neuronal circuitry and their modulation of depression, executive function and reward processing

Neuroanatomical characteristics of the serotonergic and dopaminergic systems

5-HT is primarily produced in the cell bodies of neurons located in the dorsal raphe nucleus (DRN) and medial raphe



Table 1. Effects of tryptophan manipulations on executive function related tasks.

STUDY	METHODOLOGY	TASK	EFFECT OF MANIPULATION
Evers et al ¹⁰⁰	ATD	Go/no-go	No effect
Rubia et al ⁸²	ATD	Go/no-go	No effect
Helmbold et al ⁸³	ATD	Go/no-go	No effect
Gaber et al ⁸⁴	ATD	Go/no-go	Improved accuracy and reaction times
Rubinsztein et al ⁸⁵	ATD	Go/no-go	Increased number of errors
Walderhaug et al ⁸⁶	ATD	Continuous performance Test	Increased impulsive responses
Walderhaug et al ⁸⁷	ATD	Continuous performance Test	Increased impulsive responses
Worbe et al. ⁸⁸	ATD	Four-choice Serial reaction time task	Increased impulsive responses
Clark et al. ⁸⁹	ATD	Stop signal response task	No effect
Crean et al (2002) ⁹⁰	ATD	Stop signal response task	Improvement in reaction times
Dougherty et al ⁹¹	ATD	Continuous performance test (modified)	Increased impulsive responses
Dougherty et al ⁹²	ATD	Continuous performance test (modified)	Increased impulsive responses
Dougherty et al ⁹³	ATD	Continuous performance test (modified)	No effect
Gallagher et al ⁹⁵	ATD	Wisconsin card sorting test	No effect
Hughes et al ⁹⁶	ATD	Wisconsin card sorting test; tower of London	No effect
Murphy et al ⁹⁷	ATD	Reversal learning;	Increased reaction times
		Tower of London	No effect
Park et al. ⁹⁸	ATD	Tower of London	Increased thinking times
Talbot et al ⁹⁹	ATD	Reversal learning	No effect
Evers et al ¹⁰⁰	ATD	Stroop test	Improved focused attention
Finger et al ¹⁰¹	ATD	Probabilistic reversal learning	No effect
Kanen et al ¹⁰²	ATD	Probabilistic reversal learning	No effect
Schmitt et al ¹⁰³	ATD	Stroop test	Improved focused attention
Scholes et al ¹⁰⁴	ATD	Stroop test	Improved attentional control
Horacek et al ¹⁰⁵	ATD	Stroop test	No effect
Morgan et al ¹⁰⁶	Tryptophan loading	Stroop test	No effect
Thirkettle et al ¹⁶⁶	Tryptophan loading	Probabilistic reversal learning	No effect on reversal learning;
			Increased negative feedback sensitivity
Ruocco et al ¹⁰⁸	TPH1 polymorphisms	Go/no	No effect*
Neufang et al ¹¹⁰	TPH2 polymorphisms	Five choice serial time reaction task	Increased premature responses**
Reuter et al ¹¹¹	TPH2 polymorphisms	Attention network test	Increased errors in impulse control**
Strobel et al ¹¹²	TPH2 polymorphisms	Continuous performance test	Increased errors**
Osinsky et al ¹¹³	TPH2 polymorphisms	Stroop test	Slower reaction time responses**
Gong et al ¹¹⁴	TPH2 polymorphisms	Modified response inhibition test	Fewer errors ¹
Enge et al ¹¹⁵	TPH2 polymorphisms	Attention network test	Increases errors in impulse control**

*No association between TPH1 alleles and performance.

**T-allele carriers performing worse than GG homozygotes.

¹T-allele carriers performing better than GG homozygotes.

Table 2. Effects of tyrosine manipulations on executive function related tasks.

STUDY	METHODOLOGY	TASK	EFFECT OF MANIPULATION
McClean et al ¹¹⁸	APTD	Go/no-go	No effect
		Tower of London	No effect
		Decision making task	No effect
		Set-shifting task	No effect
Lythe et al ¹¹⁹	APTD	Go/no-go	No effect
		Intra/Extra dimensional set-shifting	No effect
Vrshek-Schallhorn et al ¹²⁰	APTD	Go/no-go	Increased errors
Ramdani et al ¹²³	APTD	Simon task	No effect
Vidal et al ¹²⁴	APTD	Simon task	No effect
Borwick et al ¹²⁵	APTD	Wisconsin card sorting test	Slower reaction times
Robinson et al ¹²⁶	APTD	Reversal learning	Increased errors
Colzato et al ¹²⁹	Tyrosine loading	Stop signal response task	Reduced errors
Stock et al ¹³⁰	Tyrosine loading	Simon task (modified)	Decreased conflict responses
Steenbergen et al ¹³¹	Tyrosine loading	Task switching	Reduced errors
Robson et al ¹³²	Tyrosine loading	Wisconsin card sorting test	Slower reaction times*
Colzato et al ¹³⁴	Tyrosine loading	Stop signal response task	Reduced errors**
Dennison et al ¹³⁵	Tyrosine loading	Wisconsin card sorting test	Reduced errors

*Only under high cognitive demand.

**Improvement dependent on DA genotype.

nucleus (MRN).²³ Whilst approximately 50% of DRN cells express 5-HT, this number drops to 5% for MRN neurons.²⁴ Both medial and dorsal parts of the raphe nucleus display extensive and widespread connections with sub-cortical and cortical regions of the brain. In particular, the DRN/MRN send projections to the amygdala, hypothalamus, thalamus, superior colliculus, medial prefrontal cortex (mPFC), sensorimotor cortex, caudate putamen and septum.²⁵ 5-HT neurons often co-express other neurotransmitters, most notably GABA, glutamate and nitric oxide.²⁶ DA neurons, on the other hand, whilst also mostly localized in the midbrain, can be found in the ventral tegmental area (VTA) and substantia pars compacta (SNc). These 2 regions give rise to the mesolimbic, mesocortical (originating from the VTA) and the nigrostriatal (from the SNc) pathways. More specifically, VTA DA neurons innervate the nucleus accumbens (NAc), amygdala, hippocampus and mPFC, whereas the SNc DA neurons have axonal projections with the caudate and putamen of the striatum.²³ DA neurons also co-release nitric oxide, glutamate and GABA.

Functional interactions between the serotonergic and dopaminergic system

5-HT neurons innervate DA neurons in both the VTA and SNc but also in DA terminal fields (ie, NAc, mPFC and amygdala).²³ In addition to their anatomical interactions,

administration of 5-HT agonists/antagonists, serotonin reuptake inhibitors (SSRI) and 5-HT lesioning, has been shown to modulate DA neurons activity. The response pattern of DA neurons to 5-HT is very complex and not yet fully understood, but a brief summary of the available evidence is here reported.

Early investigations in which VTA/SNc DA neurons were recorded in anaesthetized rats showed that application of 5-HT resulted in a weak inhibition of VTA DA firing and a more robust inhibition of SNc DA cells.^{27,28} Electrical stimulation of DRN cells, on the other hand, has been reported to inhibit SNc DA cells with a low firing rate, but excite others,^{29,30} whilst in VTA DA cells, the inhibition was dependent on whether these neurons were projecting to the NAc, whereas other VTA DA neurons were excited.³¹ Using optogenetic techniques, stimulation of 5-HT terminals in the VTA and SNc produced excitatory postsynaptic potentials that were larger in magnitude for SNc DA than VTA DA cells, and critically, this effect was dependent on the co-release of glutamate.³² 5-HT excitatory effects on DA neurons have also been shown to be indirectly modulated by GABA mechanisms.³³ Synaptic increase in 5-HT by SSRI administration into the VTA (but not in the SNc), has been shown to result in reduced firing rates of VTA DA cells.^{34,35} However, these results appear to be dependent upon the type of SSRI administered, the route of administration (eg, systemic vs intracerebral), dosage,

Table 3. Effects of tryptophan manipulations on reward processing related tasks.

STUDY	METHODOLOGY	TASK	EFFECT OF MANIPULATION
Cools et al ¹³⁶	ATD	Reversal learning (modified)	Decreased errors for punished trials
Crockett et al ¹³⁷	ATD	Reinforced categorization task	Improved response vigour for punished trials
Crockett et al ¹³⁸	ATD	Go/no-go (modified)	Faster reaction times in punished trials
Robinson et al. ¹³⁹	ATD	Reversal learning (modified)	Decreased errors for punished trials
Cools et al ¹⁴⁰	ATD	Cued-reinforcement task	Increased accuracy dependent on reward certainty
Campbell-Meiklejohn et al ¹⁴³	ATD	Loss-chasing game	Reduction in loss chasing decisions
Geurts et al ¹⁴⁴	ATD	Pavlovian Instrumental transfer (PIT)	Improved inhibition to aversive cues
Hebart et al ¹⁴⁵	ATD	Pavlovian Instrumental transfer (PIT)	Improved inhibition to aversive cues
Rogers et al. ¹⁴⁶	ATD	Decision making task	Disrupted discrimination of gains
Anderson et al. ¹⁴⁷	ATD	Gambling task	No effect
Demoto et al ¹⁵¹	ATD	Delayed reward choice task	Increased discounting rates
Schweighofer et al ¹⁵²	ATD	Delayed reward choice task	Increased discounting rates
Tanaka et al ¹⁵³	ATD/tryptophan loading	Delayed reward choice task	Correlation of ATD/trypt load with reward prediction at different timescales and striatal activity
Worbe et al ¹⁵⁴	ATD	Slip of action task	Increased habitual responses
Tanaka et al ¹⁵⁶	Tryptophan loading	Decision making task	No effect

Table 4. Effects of tyrosine manipulations on reward processing related tasks.

STUDY	METHODOLOGY	TASK	EFFECT OF MANIPULATION
Hebart et al ¹⁴⁵	APTD	Pavlovian Instrumental transfer (PIT)	Impaired PIT for appetitive cues
Leyton et al ¹⁵⁹	APTD	Go/no-go	Increased commission errors for correct responses
Bjork et al ¹⁶⁰	APTD	Monetary incentive delay	No behavioural effect but correlation between reduced NAc activity and anticipation of rewards
Nagano-Saito et al ¹⁶¹	APTD	Motion discrimination task	No behavioural effect but correlation between reduced corticostriatal activity and anticipation of rewards
Frank et al ¹⁶²	APTD	Food reward (wanting/liking)	No behavioural effect but reduced striatal activity
Kelm et al ¹⁶³	APTD	Delay discounting	Increased discounting rates*
De Wit et al ¹⁶⁵	APTD	Slip of action task	Increased habitual responses

*Only in COMT val/val homozygous.

and whether the SSRI was given acutely or chronically. The effects of 5-HT lesions on VTA/SNc DA cells have produced mixed results, with both no changes in the firing rates of VTA/SNc DA cells, excitations and inhibitions.³⁶⁻³⁸ In addition to the complexities cited above, there is an abundant literature on the effect that different 5-HT receptors have on DA release, which demonstrate that DA signalling is affected by 5-HT receptor subtype (eg, 5-HT_{1a}, 5-HT_{1b}, 5-HT₂, 5-HT₃, 5-HT₄, 5-HT₅, 5-HT₆, 5-HT₇), DA target (eg, VTA vs SNc) and

their reciprocal afferent/efferent connections, reviewed extensively elsewhere²³ and outside the scope of this paper.

Regulation of mood, reward processing and executive function by the serotonergic and dopaminergic system

As reported in the previous section, administration of SSRI affects DA cells activity. Using a variety of animal models of

depression, accumulating evidence points to a shared role of 5-HT and DA in the aetiology of this mood disorder. For example, in the chronic mild stress test which attempts to mimic the symptoms of anhedonia, administration of antidepressants that are selective for 5-HT_{2c} receptors, ameliorated performance and resulted in increased DA release in the NAc.^{39,40} Critically, when D2/D3 receptors were blocked, the beneficial effects of 5-HT_{2c} stimulation on anhedonia were nullified.⁴¹ In studies of monoamine transporter knockouts for both dopamine (DAT) and serotonin (SERT), impairments have been reported in measures of behavioural despair (ie, tail suspension test and forced swimming test) and anhedonia (ie, sucrose preference test).^{42,43} Furthermore, the involvement of the mesolimbic DA pathway in regulating mood and depressive-like behaviour outside of interactions with 5-HT has been well documented in the context of the transcription factor CREB, the opioid receptor dynorphin, the protein BDNF, hypothalamic peptides and circadian genes, as extensively reviewed by Nestler and Carlezon.⁴⁴

Given that many depressive symptoms as defined by the DMS-5 could be described as impairments in reward processing (ie, a lack of motivation to obtain rewards; inability to experience pleasure; deficits in reinforcement learning),⁴⁵ it is perhaps not surprising that both 5-HT and DA would regulate its function. Deficits in the ability to predict and anticipate a reward (a core aspect of reinforcement learning), as seen in depressed patients, have been ascribed to dysfunction within the mesolimbic DA pathway.⁴⁶⁻⁵¹ Similarly, SSRI intake in healthy volunteers has been shown to diminish effort cost (ie, it increased motivation) which in turn mediated the ability to obtain more rewards.⁵² Importantly, this SSRI effect might have been driven by increasing DA activity in the ventral striatum, a brain region known to be involved in reward processing.⁵³

In addition to the functional connection between mood disorders and reward processing as modulated by the serotonergic and dopaminergic systems, several lines of evidence suggest that those suffering from depression display impairments in cognition and, in particular, executive function. A meta-analysis by McDermott and Ebmeier,⁵⁴ reported significant negative correlations between increased depressive symptom severity and decreased executive function performance, in domains that included cognitive flexibility, planning, set-shifting and working memory.

In healthy populations and based on animal studies, the serotonergic system has been implicated in the regulation of response inhibition and reversal learning (mostly through the orbitofrontal cortex), whilst the dopaminergic system in measures of cognitive flexibility which include set-shifting (via the medial prefrontal cortex).³

The acute tryptophan depletion procedure (cellular mechanisms)

One of the first attempts to lower 5-HT in humans was performed using an inhibitor of TH (PCPA). The authors found that administration of PCPA induced relapse in depression in

patients who had reported improvements in depression severity following antidepressant treatment (by a MAO inhibitor and a tricyclic compound),⁵⁵ suggesting that PCPA may have counteracted the increasing 5-HT function of the antidepressants.⁵⁶ At around the same time, a version of the current ATD procedure (in humans) was initially tested in rats. In this investigation, the animals consumed a diet that was deficient in tryptophan. This manipulation resulted in lower plasma and brain tryptophan as well as serotonin and 5-hydroxyindoleacetic acid (found in the cerebrospinal fluid [CSF] and a marker of brain serotonin synthesis).⁵⁷ Further investigations revealed that tryptophan depletion was dependent on protein synthesis, since administration of a protein synthesis inhibitor could block the fall in tryptophan depletion levels by the ATD procedure.^{58,59} In humans, the first demonstration that tryptophan levels could be lowered was shown by the Concu group,⁶⁰ who gave participants a tryptophan free mixture which resulted in reduced serum tryptophan and increased anxiety compared to a group who consumed a tryptophan balanced mixture. Several studies following the original Concu investigation have confirmed that the ATD procedure lowers serotonin synthesis in the brain,⁶¹ and additionally, the rate of 5-hydroxyindoleacetic acid in the CSF.⁶²⁻⁶⁶

What remains to be established, at the very least in humans, is whether the ATD procedure results in reductions in 5-HT release (in rats using microdialysis these reductions were dependent upon the coadministration of 5-HT reuptake inhibitors).⁶⁷ It is not clear, for example, whether decreases in 5-HT synthesis would correspond to linear decreases in 5-HT firing and/or release. One factor that is unrelated to 5-HT synthesis in the regulation of 5-HT firing is behavioural arousal and/or motor activity.⁶⁸ It is also likely that the degree of 5-HT release/firing altered by the ATD procedure would vary by brain location.^{56,61} Unrelated to 5-HT release, the ATD procedure may result in effects that are not directly related to 5-HT, including changes in BDNF,⁶⁹ amino acid balance,⁷⁰ melatonin,⁷¹ and nitric oxide synthase.^{72,73}

The acute phenylalanine and tyrosine depletion procedure (cellular mechanisms)

It was again the Biggio group in 1976 who were the first to attempt to lower DA in animals in what we now describe as the APTD procedure. Using an amino acid mixture lacking tyrosine and phenylalanine, they demonstrated in rats that tyrosine in serum and in the brain (basal ganglia specifically) could be lowered by 73% 2 hours post ingestion.⁷⁴ The exclusion of phenylalanine is required as this amino acid can be converted to tyrosine or tyrosine hydroxylase.⁷⁵ M and J Fernstrom replicated Biggio's findings two decades later.⁷⁶ The authors demonstrated that serum tyrosine and hypothalamic tyrosine levels could decrease significantly for 60 to 180 minutes due to the APTD. A year later, it was Sheehan and colleagues to confirm in humans that tyrosine plasma levels could be lowered by up to 50% over a 5-hour period by the APTD.⁷⁷ As for the ATD

procedure, there is lack of evidence in humans that the APTD can result in reductions in DA release. Using microdialysis in rats, however, McTavish and colleagues showed that the APTD decreased extracellular DA release in the striatum when amphetamine was co-administered.⁷⁸ Interestingly, DA release did not change under basal conditions (ie, when comparing APTD to control), in a manner that resembles the 5-HT release by the 5-HT reuptake inhibitors,⁶⁷ suggesting that there are specific concentration thresholds of DA and 5-HT that are necessary in order to see declines in extracellular release of these neurotransmitters under APTD and ATD. The McTavish study was also particularly important as it revealed that noradrenergic release was not affected by the APTD-amphetamine combination, indicating that the APTD preferentially affects DA neurons despite tyrosine and phenylalanine acting as molecular precursors to DA, noradrenaline and adrenaline.

The role of tryptophan in executive functions

ATD studies

The bulk of the evidence regarding the role of tryptophan in executive functions has been revealed by ATD studies. The three main cognitive domains that have been investigated are response inhibition, selective attention/cognitive interference and reversal learning. As one might expect, not all studies have administered the same cognitive task to assess a particular cognitive domain. In response inhibition studies, for example, the tests used include the Go/Nogo task, the Stop Signal task, the Continuous Performance Test, the 5-choice serial reaction time task, the Simon task, the loss avoidance in a decision-making task. Although one can assume a degree of similarity in the way all of these tasks are encoded by fronto-striatal neural circuitry,⁷⁹ it is plausible that there might be subtle differences in neural activation (not precisely captured by functional neuroimaging studies) as a result of these tasks which may account for diverging outcomes. Most of the studies reviewed here only reported behavioural effects, however there were a handful of examples in which both neuroimaging and behavioural data was gathered, which are going to help us define the neuronal networks involved.

In a study assessing response inhibition using the Go/Nogo task, the authors found that the ATD had no impact on brain activity in relation to response inhibition, however, the ATD did reduce dorsolateral prefrontal cortex activity during performance monitoring.⁸⁰ In the Go/Nogo task, response inhibition is measured as the percentage of correct responses during Go and Nogo trials. Performance monitoring, on the other hand, is assessed by measuring the reaction times on a correct response following an error, a well-known form of post-error slowing,⁸¹ which can also be measured by administering a reversal learning task. In contrast to the above findings, Rubia and colleagues, also using the Go/Nogo task, did report a neural effect of the ATD during response inhibition with reduced right

orbitoinferior (OFC) prefrontal and increased superior and medial temporal cortices activation.⁸² Evers and colleagues speculated that the reasons for the contrasting findings may relate to task difficulty of the Go/Nogo task, performance feedback

provided during the task and gender differences between their study and that of Rubia et al. Behaviourally, both reports did not find an effect of the ATD on response inhibition and performance monitoring. This is collaborated by an additional report in which no behavioural effect was found, however, during the Nogo (punishment) trials healthy female volunteers had reduced medial OFC and anterior cingulate cortex (ACC) activation compared to controls.⁸³ In contrast to these findings, a body-weight adjusted ATD experiment found improvements in accuracy and reaction times in the same task by reductions in tryptophan levels,⁸⁴ and opposite findings have been reported in another.⁸⁵ Overall, it would seem that whilst several of these prefrontal regions process stimuli that relate to the Go/Nogo task, their activation is not causally related to performance. Moreover, the behavioural evidence is mixed with a combination of null findings, improvements and impairments following ATD administration.

Behaviourally, two studies (by the same research group) that adopted the Continuous Performance Test to measure response inhibition have both found that the ATD impaired performance^{86,87}; a similar impairment was reported when the 5-choice serial reaction time task was adopted.⁸⁸ In contrast, two studies that assessed response inhibition using the Stop Signal task found either no effect of the ATD on performance,⁸⁹ or even an improvement on the stop reaction time by the ATD.⁹⁰ These data again indicate that different cognitive tasks measuring response inhibition (underpinned by similar but not identical neurobiological mechanisms) likely contribute to the relative heterogeneity of the findings.

Using a modified version of the Continuous performance task, Dougherty and colleagues, showed that those in the ATD conditions had significantly impaired performance compared to baseline (ie, prior to ATD) and to those in the tryptophan loading group⁹¹. This finding was also replicated in a follow up study both in reference to baseline and to placebo.⁹² In a third study by the same group, the authors investigated the interaction between alcohol consumption and ATD and found that the ATD combined with alcohol did not increase/decrease response inhibition.⁹³

In a separate study measuring 'Reflection Impulsivity', that is, making decisions before having gathered enough information, the Trevor Robbins' lab showed that the ATD did not affect reflection impulsivity, but rather it promoted avoidance of small, immediate (reward) losses,⁹⁴ and hence appeared to have a more specific role in aversive processing.

In a study assessing set-shifting (Wisconsin Card Sorting test), ATD administration had no impact on performance.⁹⁵ The same research group replicated these findings in a separate investigation, including no effect of the ATD on planning

abilities (as measured by the Tower of London test).^{96,97} This is interesting given that set-shifting is a subset of cognitive flexibility and suggests a possible separation of tryptophan effects on different measures of cognitive flexibility. Nevertheless, a separate research group demonstrated that the ATD can negatively impact planning abilities in the Tower of London test but only in those familiar with the task, suggesting a specific detrimental effect on performance retrieval rather than acquisition learning.⁹⁸

The ATD has also been reported to negatively impact reversal learning,⁹⁷ but a later study failed to replicate the reversal learning impairment.⁹⁹ The effect of tryptophan on *probabilistic* reversal learning (PRL), a form of reversal learning which can assess negative feedback sensitivity (a measure of switching behaviour during the task when misleading feedback has been provided) has also been tested in three additional studies. None of these studies reported a significant effect of ATD on PRL performance.¹⁰⁰⁻¹⁰²

Using the Stroop test, three investigations reported improvements in selective attention following ATD administration,^{100,103,104} with the ATD increasing the BOLD signal in the anterior cingulate cortex (ACC) and precuneus. A fourth study did not find a behavioural effect but did report increased activation in the ACC and PFC.¹⁰⁵

Taken together, the evidence reviewed suggests a potential role for tryptophan and the prefrontal cortex (PFC) (as a whole) in modulating *some forms* of response inhibition, which is in line with studies that have identified serotonin, more generally, and the prefrontal cortex in the regulation of response inhibition. Furthermore, tryptophan seems to modulate cognitive interference/selective attention but not reversal learning.

Tryptophan loading studies

There has been a real scarcity of tryptophan loading studies assessing executive function in *healthy* (several more studies have been published in clinical samples) participants. To the best of the author's knowledge, this was a study by Morgan and colleagues who administered tryptophan and found decreased activations in prefrontal regions with no behavioural effect on a cognitively demanding Stroop task.¹⁰⁶ The second study was a recent investigation by our research group in which we reported an increase in negative feedback sensitivity but no change in reversal learning as a result of tryptophan loading (compared to a placebo group).

TPH1 and TPH2 studies

Studies for TPH1 and TPH2 genes have been grouped together with the caveat that TPH1 and TPH2 are differentially expressed in the brain,¹⁰⁷ and therefore careful interpretation of the data needs to be applied.

In a study using the Go/Nogo task, the authors tested the hypothesis that single nucleotide polymorphisms in the *TPH1* gene, would affect brain activation and performance on the task.

The authors found no behavioural evidence for this but did show that those with the 'risk' allele for TPH1 had reduced medial prefrontal cortex activity during response inhibition.¹⁰⁸ Importantly, the 'risk' allele for TPH1 has been linked to lower serotonin turnover.¹⁰⁹ A different research group, instead, looked at the effect of single nucleotide polymorphisms in the *TPH2* gene on the 5-choice serial reaction time task and brain activity. Here, the authors found that the risk allele (T/T homozygous on the 703 polymorphism) resulted in a greater number of premature responses (a form of inhibitory control and/or 'waiting impulsivity') which was related to diminished ventromedial prefrontal cortex activity.¹¹⁰ Deficits in response inhibition and impulse control have also been reported on the same T/T genotype of TPH2 by 3 separate research groups,¹¹¹⁻¹¹³ despite a contradictory finding by a fourth in which however the T/T and G/T genotypes were grouped together and compared to the G/G.¹¹⁴ Using EEG recordings, Enge et al were able to reveal some of the putative mechanisms by which response inhibition performance is superior in the G-allele versus T-allele homozygotes in that those with the G-allele displayed increased event-related gamma-band activity during the task.¹¹⁵ Critically, gamma-band activity has been reported to modulate top-down attentional selection by amplifying relevant sensory inputs and inhibiting attention to irrelevant ones,^{116,117} hence facilitating response selection.

The role of tyrosine in executive functions

Tyrosine depletion studies

The first use of the APTD procedure to understand the impact of reductions in putative dopaminergic synthesis on executive function in healthy volunteer was a study conducted by McLean et al. Using a parallel group design (crossover repeated measures can be problematic with the APTD due to the unpalatability of the amino acid drinks and the potential for a high withdrawal rate between repeated sessions), the APTD did not affect measures of planning, decision making and set-shifting compared to the balanced (control) group.¹¹⁸ These findings were largely replicated by Lythe and colleagues (this time using a crossover repeated measure design) as neither set-shifting nor response inhibition nor impulsivity were significantly affected by the APTD.¹¹⁹ Response inhibition was negatively affected by the APTD as reported in a later study,¹²⁰ however, it is worth noting that the statistical analyses contained multiple comparisons (ie, a total of 14 measures for the response inhibition task were taken) which did not appear to control for false discovery rate such as by the application of the Benjamini-Hochberg adjustment, as recommended elsewhere.¹²¹ Response inhibition as measured by the Simon task was unaffected by the APTD in two additional studies,^{122,123} nevertheless, changes in the N-40 component (an event related potential which has been proposed to represent response selection)¹²⁴ by the APTD were noted but these neurophysiological changes were unrelated to behavioural performance. In a recent study by our research group, we reported a negative effect of the

APTD on task-switching using the Wisconsin Card Sorting Task, an effect which could be 'rescued' by anodal (ie, excitatory) transcranial direct current stimulation (tDCS) of the dorsolateral prefrontal cortex,¹²⁵ highlighting a potential neuronal network which may underpin APTD effects on task-switching. On the contrary, Robinson and colleagues demonstrated that the APTD had a beneficial effect on reversal learning in healthy female participants but not in males.¹²⁶ This improvement in females was driven by increased sensitivity in punishment processing following an error during reversal trials. These results parallel some of the findings reported in the ATD literature.

Tyrosine loading studies

In contrast to the APTD studies where the overall pattern of results would suggest that being tyrosine depleted does not affect executive function (but see),¹²⁴ tyrosine loading studies have been characterized by more consistent results. A plausible explanation for this difference may lie in the degree to which the APTD suppresses DA availability in contrast to the increases in DA availability by tyrosine loading. That is, both theoretical and experimental evidence support the view of an inverted-U shaped function between DA and cognitive function, whereby too low or too high levels of DA may lead to detrimental performance, with an optimal level occurring somewhere in the middle and providing the most (cognitive/behavioural) benefits.¹²⁷ Whilst APTD studies have used largely similar amino acids concentrations, the same cannot be said for tyrosine loading studies where dosages have varied from as little as 500 mg to 12 g.¹²⁸ Therefore, it is possible that the 50% reductions in plasma tyrosine levels by the APTD as reported by Sheehan and colleagues,⁷⁷ may not always be sufficient to create a dip in DA availability that is on the left-bottom side of the inverted-U curve. On the contrary, the combination of more varied dosages in tyrosine loading studies and the fact that tyrosine conversion to dopamine is limited by the competition from other endogenous amino acids and by the TH enzyme, means that even when higher dosages of tyrosine have been administered, these are unlikely to result in DA availability that is on the right-bottom side of the inverted-U curve.¹²⁸

Two studies by the Colzato group demonstrated an improvement in two separate measures of response inhibition by tyrosine supplementation when compared to a placebo group.^{129,130} Similar results were obtained when measuring task switching.¹³¹ Interestingly, our research group found that when task switching was measured under cognitively demanding conditions (ie, after having completed a digit spat memory task), tyrosine was unable to enhance performance.¹³² Previous studies have demonstrated that under stressful, demanding situations, catecholamine activity is increased, depleting neurotransmitter levels.¹³³ In line with the inverted-U shaped

hypothesis of DA function and cognitive performance, we speculated that tyrosine supplementation in our study was insufficient to replenish catecholamine levels to improve task-switching above baseline. This view is reinforced by an additional study in which tyrosine supplementation was beneficial to response inhibition performance only in those who were T/T homozygotes in the DA D2 receptor gene and hence with lower baseline striatal DA levels,¹³⁴ compared to C/C homozygotes with higher striatal DA levels. Finally, our tDCS findings in relation to anodal stimulation of the dlPFC, the APTD and cognitive flexibility (task-switching),¹²⁴ were replicated in another study where tyrosine administration improved cognitive flexibility (over placebo), but this effect could be 'nullified' by cathodal (inhibitory) stimulation of the dlPFC.¹³⁵

The role of tryptophan in reward processing

ATD studies

As discussed in a previous section accumulating evidence suggests that deficits in the regulation of mood (eg, depression) may be related to impairments in executive function, and reward processing. The latter will be discussed in this section with reference to ATD studies.

In a series of studies by the Cools and Robbins group using both instrumental and Pavlovian tasks that allowed to separate reward processing from punishment, the authors reported that the ATD facilitated prediction for punishment but not for reward.¹³⁶⁻¹⁴⁰ Neuroanatomically, neural responses to negative outcomes (eg, losses) by the ATD have been reported in the dorsomedial prefrontal cortex and amygdala.¹⁴¹ The findings by the Cools and Robbins group have been confirmed by a number of investigations, whereby the ATD worsened performance for goal-directed behaviour under reinforcement but improved it for goal-directed punishment (ie, the avoidance of loss),^{142,143} and by studies on Pavlovian-instrumental transfer (PIT) looking at appetitive and aversive outcomes.^{144,145} However, an investigation by Rogers and colleagues only reported an impairment for reward but no improvement for punishment prediction,¹⁴⁶ similar to reports in either probability discounting,¹⁴⁷ counterfactual learning,¹⁴⁸ and a risk-seeking task.¹⁴⁹ Additionally, in a decision making task, the ATD reduced vmPFC activity in relation to reward outcome but not to punishment avoidance.¹⁵⁰

In support of the idea that tryptophan is not only important for punishment prediction but also reward representation, a series of pivotal studies by the Doya group demonstrated that the ATD affects reward discounting. More specifically, Doya and colleagues found that tryptophan depletion led to a preference for small, immediate rewards over larger delayed rewards.¹⁵¹⁻¹⁵³ Moreover, in a separate ATD/loading study, Doya and colleagues demonstrated that whilst low tryptophan levels (induced by the ATD) correlated with encoding of reward

prediction errors at short timescales, higher levels of tryptophan (induced by tryptophan loading) were correlated with prediction errors at longer timescales.¹⁵³ These results complement the extensive literature on the role of DA in reward prediction error (ie, the difference between expected and obtained reward) and add the dimension of timing to the way in which rewards are encoded. Finally, Worbe and colleagues showed that the ATD produced a shift from goal-directed behaviour to habitual like responses,¹⁵⁴ a finding that resembles manipulations of the dopaminergic system in the striatum.¹⁵⁵

Tryptophan loading studies

As for the scarcity of studies reported using tryptophan loading in the context of executive function in healthy populations (see section 5b), a similar pattern emerged for reward processing. Again, to the best of the author's knowledge, only two publications could be found both by the Doya group. In the first study, tryptophan loading was correlated with prediction errors at longer timescales.¹⁵³ In the second, tryptophan loading neither affected learning from delayed punishments or delayed rewards.¹⁵⁶

TPH1 and TPH2 studies

There were no studies that isolated the effects of either TPH1 or TPH2 polymorphisms in healthy volunteers and tested these in experimental cognitive tasks that measure reward processing. In two cases, a composite measure of the 5-HTTLPR (S allele) (and TPH2-703 (G allele) genes was related to diminished altruistic punishment (ie, 'impulsive response to perceived provocation resulting from uncooperative behaviour'),¹⁵⁷ whereas in a second study, the combination of polymorphisms from the candidate genes TPH2, HRTR2A and HRTR1A was related to differences in reward sensitivity.¹⁵⁸

The role of tyrosine in reward processing

Tyrosine depletion studies

In line with extensive evidence from animal studies of the role of DA in reward processing, several APTD investigations in healthy volunteers have replicated these findings. For example, in a study by Hebart and Glasher,¹⁴⁵ the APTD selectively impaired PIT for appetitive cues, consistent with the established role of dopamine in reward prediction. The APTD has also been reported to affect incentive salience and motivation for reinforcement which again mirrors the animal literature. Leyton and colleagues found that the APTD reduced the ability to respond to stimuli that predicted reward, and that co-administration of L-Dopa (a DA agonist) could prevent this impairment.¹⁵⁹ Moreover, Bjork et al using fMRI were able to pinpoint the neuronal signal that was responsible for reduced processing of appetitive cues. NAc activity was reduced following APTD administration when participants were viewing cues that

anticipated high rewards.¹⁶⁰ A similar finding was reported by Nagano-Saito et al at a neuronal network, although the APTD did not affect behavioural performance.¹⁶¹ These neuroimaging results were consistent in a third study by Frank and colleagues,¹⁶² who furthermore tested whether body mass index (BMI) may mediate this response, given that reward sensitivity and DA alterations are associated with obesity. The authors did not find a mediation effect of BMI on reward processing, suggesting that other factors in obesity may be at play in determining reward-related responses. Kelm and Bottinger, on the other hand, reported a genetic \times APTD interaction in reward processing. More specifically, the authors found¹⁶³ that those homozygous for the val/val allele of the COMT genotype (encoding an enzyme that degrades extracellular DA particularly in the prefrontal cortex), and that were administered the APTD displayed increased impulsive choice for immediate rewards. Val/val individuals are known to have the lowest level of DA activity¹⁶⁴ (compared to val/met and met/met), and these findings therefore demonstrate that the combination of reduced DA synthesis by the APTD coupled with lower baseline levels of DA activity in the val/val COMT genotype negatively impacted performance as previously suggested by the theory of an inverted-U shaped function with respect to DA and cognition.

Finally, de Wit and colleagues replicated the findings of Worbe et al for the ATD, in that the APTD also produced a similar shift from goal-directed to habitual like responses in a reinforcement task.¹⁶⁵

Tyrosine loading studies

No studies assessing the impact of tyrosine loading on reward processing tasks in healthy volunteers could be found.

Conclusion and future research

Accumulating evidence over the past three decades has identified the serotonergic precursor tryptophan and the dopaminergic precursor tyrosine as involved in the regulation of executive function and reward processing.

The key take home point of this review is that the functional interactions that occur at the cellular and neuronal network level between the 5-HT and DA system contribute to a shared role of tryptophan and tyrosine in various subcomponents of both executive and reward processing, despite some clear differentiation. For both tryptophan and tyrosine related studies, there remains a substantial research gap which would need to address how the ATD/tryptophan loading and the APTD/tyrosine loading procedures affect 5-HT and DA release in the human brain. Nevertheless, neuroimaging (mostly in the form of fMRI), genetic, and non-invasive brain stimulation investigations have started to pave the way for a more comprehensive understanding of the mechanisms by which tryptophan and tyrosine affect executive function and reward processing.

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REFERENCES

- Cowen PJ, Browning M. What has serotonin to do with depression? *World Psychiatry* 2015;14:158-160.
- Baba S, Murai T, Nakako T, et al. The serotonin 5-HT_{1A} receptor agonist tandospirone improves executive function in common marmosets. *Behav Brain Res.* 2015;287:120-126.
- Logue SF, Gould TJ. The neural and genetic basis of executive function: attention, cognitive flexibility, and response inhibition. *Pharmacol Biochem Behav.* 2014;123:45-54.
- Madsen K, Erritzoe D, Mortensen EL, et al. Cognitive function is related to fronto-striatal serotonin transporter levels—a brain PET study in young healthy subjects. *Psychopharmacology.* 2011;213:573-581.
- Pennanen L, van der Hart M, Yu L, Tecott LH. Impact of serotonin (5-HT)_{2C} receptors on executive control processes. *Neuropsychopharmacology.* 2013;38:957-967.
- Pokorny T, Duerler P, Seifritz E, Vollenweider FX, Preller KH. LSD acutely impairs working memory, executive functions, and cognitive flexibility, but not risk-based decision-making. *Psychol Me.* 2019;1-10. doi:10.1017/S0033291719002393.
- Puig MV, Gullledge AT. Serotonin and prefrontal cortex function: neurons, networks, and circuits. *Mol Neurobiol.* 2011;44:449-464.
- Skandali N, Rowe JB, Voon V, et al. Dissociable effects of acute SSRI (escitalopram) on executive, learning and emotional functions in healthy humans. *Neuropsychopharmacology.* 2018;43:2645-2651.
- Dalley JW, Roiser JP. Dopamine, serotonin and impulsivity. *Neuroscience.* 2012;215:42-58.
- Bailey MR, Williamson C, Mezas C, et al. The effects of pharmacological modulation of the serotonin 2C receptor on goal-directed behavior in mice. *Psychopharmacology.* 2016;233:615-624.
- Balasuubramani PP, Chakravarthy VS, Ravindran B, Moustafa AA. An extended reinforcement learning model of basal ganglia to understand the contributions of serotonin and dopamine in risk-based decision making, reward prediction, and punishment learning. *Front Comput Neurosci.* 2014;8:47.
- Eskenazi D, Neumaier JF. Increased expression of the 5-HT₆ receptor by viral mediated gene transfer into posterior but not anterior dorsomedial striatum interferes with acquisition of a discrete action–outcome task. *J Psychopharmacol.* 2011;25:944-951.
- Eskenazi D, Neumaier JF. Increased expression of 5-HT₆ receptors in dorso-lateral striatum decreases habitual lever pressing, but does not affect learning acquisition of simple operant tasks in rats. *Eur J Neurosci.* 2011;34:343-351.
- Iigaya K, Fonseca MS, Murakami M, Mainen ZF, Dayan P. An effect of serotonergic stimulation on learning rates for rewards apparent after long intertrial intervals. *Nat Commun.* 2018;9:2477.
- Miyazaki K, Miyazaki KW, Doya K. Activation of dorsal raphe serotonin neurons underlies waiting for delayed rewards. *J Neurosci.* 2011;31:469-479.
- Nakamura K. The role of the dorsal raphe nucleus in reward-seeking behavior. *Front Integr Neurosci.* 2013;7:60.
- Aquili L. The causal role between phasic midbrain dopamine signals and learning. *Front Behav Neurosci.* 2014;8:139.
- Furlong RA, Rubinsztein JS, Ho L, et al. Analysis and metaanalysis of two polymorphisms within the tyrosine hydroxylase gene in bipolar and unipolar affective disorders. *Am J Med Genet.* 1999;88:88-94.
- Persson M-L, Wasserman D, Jönsson EG, et al. Search for the influence of the tyrosine hydroxylase (TCAT) n repeat polymorphism on personality traits. *Psychiatry Res.* 2000;95:1-8.
- Thibaut F, Ribeyre J-M, Dourmap N, et al. Association of DNA polymorphism in the first intron of the tyrosine hydroxylase gene with disturbances of the catecholaminergic system in schizophrenia. *Schizophr Res.* 1997;23:259-264.
- Dahmen N, Völz M, Singer P, Hiemke C, Szegedi A. Tyrosine hydroxylase Val-81-Met polymorphism associated with early-onset alcoholism. *Psychiatr Genet.* 2005;15:13-16.
- Persson M-L, Wasserman D, Geijer T, Jönsson EG, Terenius L. Tyrosine hydroxylase allelic distribution in suicide attempters. *Psychiatry Res.* 1997;72:73-80.
- De Deurwaerdere P, Di Giovanni G. Serotonergic modulation of the activity of mesencephalic dopaminergic systems: Therapeutic implications. *Prog Neurobiol.* 2017;151:175-236.
- Jacobs BL, Azmitia EC. Structure and function of the brain serotonin system. *Physiol Rev.* 1992;72:165-229.
- Hale MW, Lowry CA. Functional topography of midbrain and pontine serotonergic systems: implications for synaptic regulation of serotonergic circuits. *Psychopharmacology.* 2011;213:243-264.
- Hioki H, Nakamura H, Ma Y-F, et al. Vesicular glutamate transporter 3-expressing nonserotonergic projection neurons constitute a subregion in the rat midbrain raphe nuclei. *J Comp Neurol.* 2010;518:668-686.
- Aghajanian G, Bunney B. Dopaminergic and non-dopaminergic neurons of the substantia nigra: differential responses to putative transmitters. *Neuropsychopharmacology.* 1975;359:444-452.
- Dray A, Gonye TJ, Oakley NR, Tanner T. Evidence for the existence of a raphe projection to the substantia nigra in rat. *Brain Res.* 1976;113:45-57.
- Gervais J, Rouillard C. Dorsal raphe stimulation differentially modulates dopaminergic neurons in the ventral tegmental area and substantia nigra. *Synapse.* 2000;35:281-291.
- Kelland MD, Freeman A, Chiodo L. Serotonergic afferent regulation of the basic physiology and pharmacological responsiveness of nigrostriatal dopamine neurons. *J Pharmacol Exp Ther.* 1990;253:803-811.
- Kelland MD, Freeman AS, Rubin J, Chiodo LA. Ascending afferent regulation of rat midbrain dopamine neurons. *Brain Res Bull.* 1993;31:539-546.
- Wang H, Cachoche R, Cheer J, Morales M. Dorsal raphe excitatory drive on VTA dopamine neurons. Paper presented at: Soc Neurosci Abstr 2012.
- Pessia M, Jiang Z-G, Alan North R, Johnson SW. Actions of 5-hydroxytryptamine on ventral tegmental area neurons of the rat in vitro. *Brain Res.* 1994;654:324-330.
- Di Mascio M, Esposito E. The degree of inhibition of dopaminergic neurons in the ventral tegmental area induced by selective serotonin reuptake inhibitors is a function of the density-power-spectrum of the interspike interval. *Neuroscience.* 1997;79:957-961.
- Di Matteo V, Di Giovanni G, Di Mascio M, Esposito E. Selective blockade of serotonin 2C/2B receptors enhances dopamine release in the rat nucleus accumbens. *Neuropharmacology.* 1998;37:265-272.
- Guiard BP, El Mansari M, Merali Z, Blier P. Functional interactions between dopamine, serotonin and norepinephrine neurons: an in-vivo electrophysiological study in rats with monoaminergic lesions. *Int J Neuropsychopharmacol.* 2008;11:625-639.
- Minabe Y, Emori K, Ashby Jr CR. The depletion of brain serotonin levels by para-chlorophenylalanine administration significantly alters the activity of midbrain dopamine cells in rats: An extracellular single cell recording study. *Synapse.* 1996;22:46-53.
- Prisco S, Esposito E. Differential effects of acute and chronic fluoxetine administration on the spontaneous activity of dopaminergic neurons in the ventral tegmental area. *Br J Pharmacol.* 1995;116:1923-1931.
- Di Matteo V, Di Mascio M, Di Giovanni G, Esposito E. Acute administration of amitriptyline and mianserin increases dopamine release in the rat nucleus accumbens: possible involvement of serotonin(2C) receptors. *Psychopharmacology.* 2000;150:45-51.
- Moreau JL, Bourson A, Jenck F, Martin JR, Mortas P. Curative effects of the atypical antidepressant mianserin in the chronic mild stress-induced anhedonia model of depression. *J Psychiatry Neurosci.* 1994;19:51-56.
- Willner P. Animal models of depression: evidence of validity and applications. *Adv biochem psychopharmacol.* 1995;49:19-41.
- Perona MT, Waters S, Hall FS, et al. Animal models of depression in dopamine, serotonin and norepinephrine transporter knockout mice: prominent effects of dopamine transporter deletions. *Behav pharmacol.* 2008;19:566.
- Wellman C, Izquierdo A, Garrett J, et al. Impaired stress-coping and fear extinction and abnormal corticolimbic morphology in serotonin transporter knock-out mice. *J Neurosci.* 2007;27:684-691.
- Nestler EJ, Carlezon WA. The Mesolimbic Dopamine Reward Circuit in Depression. *Biol Psychiatry.* 2006;59:1151-1159.
- Cléry-Melin M-L, Jollant F, Gorwood P. Reward systems and cognitions in Major Depressive Disorder. *CNS Spectr.* 2019;24:64-77.
- Admon R, Kaiser RH, Dillon DG, et al. Dopaminergic enhancement of striatal response to reward in major depression. *Am J Psychiatry.* 2017;174:378-386.
- Delgado MR. Reward-related responses in the human striatum. *Ann NY Acad Sci.* 2007;1104:70-88.
- Der-Avakian A, Markou A. The neurobiology of anhedonia and other reward-related deficits. *Trends neurosci.* 2012;35:68-77.
- Knutson B, Bhanji JP, Cooney RE, Atlas LY, Gotlib IH. Neural responses to monetary incentives in major depression. *Biol Psychiatry.* 2008;63:686-692.
- Ubl B, Kuehner C, Kirsch P, Ruttorf M, Diener C, Flor H. Altered neural reward and loss processing and prediction error signalling in depression. *Soc Cogn Affect Neurosci.* 2015;10:1102-1112.
- Kumar P, Waiter G, Ahearn T, Milders M, Reid I, Steele JD. Abnormal temporal difference reward-learning signals in major depression. *Brain.* 2008;131:2084-2093.
- Meyniel F, Goodwin GM, Deakin JW, et al. A specific role for serotonin in overcoming effort cost. *Elife.* 2016;5:e17282.
- Ossewaarde L, Verkes RJ, Hermans EJ, et al. Two-week administration of the combined serotonin-noradrenaline reuptake inhibitor duloxetine augments functioning of mesolimbic incentive processing circuits. *Biol Psychiatry.*

- 2011;70:568-574.
54. McDermott LM, Ebmeier KP. A meta-analysis of depression severity and cognitive function. *J Affect Disord.* 2009;119:1-8.
 55. Shopsin B, Friedman E, Gershon S. Parachlorophenylalanine reversal of tranylcypromine effects in depressed patients. *Arch Gen Psychiatry.* 1976;33:811-819.
 56. Young SN. Acute tryptophan depletion in humans: a review of theoretical, practical and ethical aspects. *J Psychiatry Neurosci.* 2013;38:294-305.
 57. Biggio G, Fadda F, Fanni P, Tagliamonte A, Gessa GL. Rapid depletion of serum tryptophan, brain tryptophan, serotonin and 5-hydroxyindoleacetic acid by a tryptophan-free diet. *Life Sci.* 1974;14:1321-1329.
 58. Moja EA, Restani P, Corsini E, Stacchezzini MC, Assereto R, Galli CL. Cycloheximide blocks the fall of plasma and tissue tryptophan levels after tryptophan-free amino acid mixtures. *Life Sci.* 1991;49:1121-1128.
 59. Oldendorf WH, Szabo J. Amino acid assignment to one of three blood-brain barrier amino acid carriers. *Am J Physiol.* 1976;230:94-98.
 60. Concu A, Fadda F, Blanco S, Congia S, Lostia M. Mental changes induced by the oral administration of tryptophan-free amino acid mixtures in man. *IRCS Med Sci.* 1977;5:520.
 61. Nishizawa S, Benkelfat C, Young SN, et al. Differences between males and females in rates of serotonin synthesis in human brain. *Proc Natl Acad Sci U S A.* 1997;94:5308-5313.
 62. Carpenter LL, Anderson GM, Pelton GH, et al. Tryptophan depletion during continuous CSF sampling in healthy human subjects. *Neuropsychopharmacology.* 1998;19:26-35.
 63. Moreno FA, McGavin C, Malan Jr TP, et al. Tryptophan depletion selectively reduces CSF 5-HT metabolites in healthy young men: results from single lumbar puncture sampling technique. *Int J Neuropsychopharmacology.* 2000;3:277-283.
 64. Moreno FA, Parkinson D, Palmer C, et al. CSF neurochemicals during tryptophan depletion in individuals with remitted depression and healthy controls. *Eur Neuropsychopharmacology.* 2010;20:18-24.
 65. Salomon RM, Kennedy JS, Johnson BW, et al. Association of a critical CSF tryptophan threshold level with depressive relapse. *Neuropsychopharmacology.* 2003;28:956-960.
 66. Williams W, Shoaf S, Hommer D, Rawlings R, Linnoila M. Effects of acute tryptophan depletion on plasma and cerebrospinal fluid tryptophan and 5-hydroxyindoleacetic acid in normal volunteers. *J Neurochem.* 1999;72:1641-1647.
 67. Stancampiano R, Melis F, Sarais L, Cocco S, Cugusi C, Fadda F. Acute administration of a tryptophan-free amino acid mixture decreases 5-HT release in rat hippocampus in vivo. *Am J Physiol.* 1997;272:R991-R994.
 68. Rueter LE, Fornal CA, Jacobs BL. A critical review of 5-HT brain microdialysis and behavior. *Rev Neurosci.* 1997;8:117-138.
 69. van Donkelaar EL, Blokland A, Ferrington L, Kelly PAT, Steinbusch HWM, Prickaerts J. Mechanism of acute tryptophan depletion: is it only serotonin? *Mol Psychiatry.* 2011;16:695-713.
 70. Gietzen DW, Rogers QR, Leung P, Semon B, Piechota T. Serotonin and feeding responses of rats to amino acid imbalance: initial phase. *Am J Physiol.* 1987;253:R763-R771.
 71. Zimmermann R, McDougle C, Schumacher M, et al. Effects of acute tryptophan depletion on nocturnal melatonin secretion in humans. *J Clin Endocrinol Metab.* 1993;76:1160-1164.
 72. Lieben C, Blokland A, Westerink B, Deutz N. Acute tryptophan and serotonin depletion using an optimized tryptophan-free protein-carbohydrate mixture in the adult rat. *Neurochem Int.* 2004;44:9-16.
 73. van Donkelaar EL, Ferrington L, Blokland A, Steinbusch HW, Prickaerts J, Kelly PA. Acute tryptophan depletion in rats alters the relationship between cerebral blood flow and glucose metabolism independent of central serotonin. *Neuroscience.* 2009;163:683-694.
 74. Biggio G, Porceddu ML, Gessa GL. Decrease of homovanillic, dihydroxyphenylacetic acid and cyclic-adenosine-3',5'-monophosphate content in the rat caudate nucleus induced by the acute administration of an amino acid mixture lacking tyrosine and phenylalanine. *J Neurochem.* 1976;26:1253-1255.
 75. Badawy AA-B, Dougherty DM, Richard DM. Specificity of the acute tryptophan and tyrosine plus phenylalanine depletion and loading tests I. Review of biochemical aspects and poor specificity of current amino acid formulations. *Int J Tryptophan Res.* 2010;3:23-34.
 76. Fernstrom MH, Fernstrom JD. Acute tyrosine depletion reduces tyrosine hydroxylation rate in rat central nervous system. *Life Sci.* 1995;57:PL97-PL102.
 77. Sheehan BD, Tharyan P, McTavish SF, Campling GM, Cowen PJ. Use of a dietary manipulation to deplete plasma tyrosine and phenylalanine in healthy subjects. *J Psychopharmacol.* 1996;10:231-234.
 78. McTavish SFB, Cowen PJ, Sharp T. Effect of a tyrosine-free amino acid mixture on regional brain catecholamine synthesis and release. *Psychopharmacology.* 1999;141:182-188.
 79. Chambers CD, Garavan H, Bellgrove MA. Insights into the neural basis of response inhibition from cognitive and clinical neuroscience. *Neurosci Biobehav Rev.* 2009;33:631-646.
 80. Evers EAT, van der Veen FM, van Deursen JA, Schmitt JAJ, Deutz NEP, Jolles J. The effect of acute tryptophan depletion on the BOLD response during performance monitoring and response inhibition in healthy male volunteers. *Psychopharmacology.* 2006;187:200-208.
 81. Jentsch I, Dudschig C. Short article: Why do we slow down after an error? Mechanisms underlying the effects of posterror slowing. *Q J Exp Psychol.* 2009;62:209-218.
 82. Rubia K, Lee F, Cleare AJ, et al. Tryptophan depletion reduces right inferior prefrontal activation during response inhibition in fast, event-related fMRI. *Psychopharmacology.* 2005;179:791-803.
 83. Helmbold K, Zvyagintsev M, Dahmen B, et al. Effects of serotonin depletion on punishment processing in the orbitofrontal and anterior cingulate cortices of healthy women. *Eur Neuropsychopharmacol.* 2015;25:846-856.
 84. Gaber TJ, Dingerkus VLS, Crockett MJ, et al. Studying the effects of dietary body weight-adjusted acute tryptophan depletion on punishment-related behavioral inhibition. *Food Nutr Res.* 2015;59:28443-28443.
 85. Rubinsztein JS, Rogers RD, Riedel WJ, Mehta MA, Robbins TW, Sahakian BJ. Acute dietary tryptophan depletion impairs maintenance of "affective set" and delayed visual recognition in healthy volunteers. *Psychopharmacology.* 2001;154:319-326.
 86. Walderhaug E, Landrø NI, Magnusson A. A synergic effect between lowered serotonin and novel situations on impulsivity measured by CPT. *J Clin Exp Neuropsychol.* 2008;30:204-211.
 87. Walderhaug E, Lunde H, Nordvik JE, Landrø N, Refsum H, Magnusson A. Lowering of serotonin by rapid tryptophan depletion increases impulsiveness in normal individuals. *Psychopharmacology.* 2002;164:385-391.
 88. Worbe Y, Savulich G, Voon V, Fernandez-Egea E, Robbins TW. Serotonin depletion induces 'waiting impulsivity' on the human four-choice serial reaction time task: cross-species translational significance. *Neuropsychopharmacology.* 2014;39:1519-1526.
 89. Clark L, Roiser JP, Cools R, Rubinsztein DC, Sahakian BJ, Robbins TW. Stop signal response inhibition is not modulated by tryptophan depletion or the serotonin transporter polymorphism in healthy volunteers: implications for the 5-HT theory of impulsivity. *Psychopharmacology.* 2005;182:570-578.
 90. Crean J, Richards JB, de Wit H. Effect of tryptophan depletion on impulsive behavior in men with or without a family history of alcoholism. *Behav Brain Res.* 2002;136:349-357.
 91. Dougherty DM, Marsh DM, Mathias CW, et al. The effects of alcohol on laboratory-measured impulsivity after l-Tryptophan depletion or loading. *Psychopharmacology.* 2007;193:137-150.
 92. Dougherty DM, Richard DM, James LM, Mathias CW. Effects of acute tryptophan depletion on three different types of behavioral impulsivity. *Int J Tryptophan Res.* 2010;3:99-111.
 93. Dougherty DM, Mullen J, Hill-Kapturczak N, et al. Effects of tryptophan depletion and a simulated alcohol binge on impulsivity. *Exp Clin Psychopharmacol.* 2015;23:109-121.
 94. Crockett MJ, Clark L, Smillie LD, Robbins TW. The effects of acute tryptophan depletion on costly information sampling: impulsivity or aversive processing? *Psychopharmacology.* 2012;219:587-597.
 95. Gallagher P, Massey AE, Young AH, McAllister-Williams RH. Effects of acute tryptophan depletion on executive function in healthy male volunteers. *BMC Psychiatry.* 2003;3:10.
 96. Hughes JH, Gallagher P, Stewart ME, Matthews D, Kelly TP, Young AH. The Effects of Acute Tryptophan Depletion on Neuropsychological Function. *J Psychopharmacol.* 2003;17:300-309.
 97. Murphy F, Smith K, Cowen P, Robbins T, Sahakian B. The effects of tryptophan depletion on cognitive and affective processing in healthy volunteers. *Psychopharmacology.* 2002;163:42-53.
 98. Park SB, Coull JT, McShane RH, et al. Tryptophan depletion in normal volunteers produces selective impairments in learning and memory. *Neuropharmacology.* 1994;33:575-588.
 99. Talbot PS, Watson DR, Barrett SL, Cooper SJ. Rapid tryptophan depletion improves decision-making cognition in healthy humans without affecting reversal learning or set shifting. *Neuropsychopharmacology.* 2006;31:1519-1525.
 100. Evers EAT, van der Veen FM, Jolles J, Deutz NEP, Schmitt JAJ. Acute tryptophan depletion improves performance and modulates the BOLD response during a Stroop task in healthy females. *Neuroimage.* 2006;32:248-255.
 101. Finger EC, Marsh AA, Buzas B, et al. The impact of tryptophan depletion and 5-HTTLPR genotype on passive avoidance and response reversal instrumental learning tasks. *Neuropsychopharmacology.* 2007;32:206-215.
 102. Kanen JW, Arntz FE, Yellowlees R, et al. Probabilistic reversal learning under acute tryptophan depletion in healthy humans: a conventional analysis. *J Psychopharmacol.* 2020;34:580-583.
 103. Schmitt JAJ, Jorissen BL, Sobczak S, et al. Tryptophan depletion impairs memory consolidation but improves focussed attention in healthy young volunteers. *J Psychopharmacol.* 2000;14:21-29.

104. Scholes KE, Harrison BJ, O'Neill BV, et al. Acute serotonin and dopamine depletion improves attentional control: findings from the stroop task. *Neuropsychopharmacology*. 2007;32:1600-1610.
105. Horacek J, Zavesicka L, Tintera J, et al. The effect of tryptophan depletion on brain activation measured by functional magnetic resonance imaging during the Stroop test in healthy subjects. *Physiol Res*. 2005;54:235-244.
106. Morgan RM, Parry AMM, Arida RM, Matthews PM, Davies B, Castell LM. Effects of elevated plasma tryptophan on brain activation associated with the Stroop task. *Psychopharmacology*. 2007;190:383-389.
107. Walther DJ, Bader M. A unique central tryptophan hydroxylase isoform. *Biochem Pharmacol*. 2003;66:1673-1680.
108. Ruocco AC, Rodrigo AH, Carcone D, McMMain S, Jacobs G, Kennedy JL. Tryptophan hydroxylase 1 gene polymorphisms alter prefrontal cortex activation during response inhibition. *Neuropsychology*. 2016;30:18-27.
109. Andreou D, Saetre P, Werge T, et al. Tryptophan hydroxylase gene 1 (TPH1) variants associated with cerebrospinal fluid 5-hydroxyindole acetic acid and homovanillic acid concentrations in healthy volunteers. *Psychiatry Res*. 2010;180:63-67.
110. Neufang S, Akhrif A, Herrmann CG, et al. Serotonergic modulation of 'waiting impulsivity' is mediated by the impulsivity phenotype in humans. *Transl Psychiatry*. 2016;6:e940-e940.
111. Reuter M, Ott U, Vaitl D, Hennig J. Impaired executive control is associated with a variation in the promoter region of the tryptophan hydroxylase 2 gene. *J Cogn Neurosci*. 2007;19:401-408.
112. Strobel A, Dreisbach G, Müller J, Goschke T, Brocke B, Lesch K-P. Genetic variation of serotonin function and cognitive control. *J Cogn Neurosci*. 2007;19:1923-1931.
113. Osinsky R, Schmitz A, Alexander N, Kuepper Y, Kozyra E, Hennig J. TPH2 gene variation and conflict processing in a cognitive and an emotional Stroop task. *Behav Brain Res*. 2009;198:404-410.
114. Gong P, Zhang F, Ge W, et al. Association analysis of TPH2, 5-HT2A, and 5-HT6 with executive function in a young Chinese Han population. *J Neurogenet*. 2011;25:27-34.
115. Enge S, Fleischhauer M, Lesch K-P, Reif A, Strobel A. Variation in key genes of serotonin and norepinephrine function predicts gamma-band activity during goal-directed attention. *Cereb Cortex*. 2012;24:1195-1205.
116. Desimone R, Duncan J. Neural mechanisms of selective visual attention. *Ann Rev Neurosci*. 1995;18:193-222.
117. Jensen O, Kaiser J, Lachaux J-P. Human gamma-frequency oscillations associated with attention and memory. *Trends Neurosci*. 2007;30:317-324.
118. McLean A, Rubinsztein JS, Robbins TW, Sahakian BJ. The effects of tyrosine depletion in normal healthy volunteers: implications for unipolar depression. *Psychopharmacology*. 2004;171:286-297.
119. Lythe KE, Anderson IM, Deakin JFW, Elliott R, Strickland PL. Lack of behavioural effects after acute tyrosine depletion in healthy volunteers. *J Psychopharmacol*. 2005;19:5-11.
120. Vrshek-Schallhorn S, Wahlstrom D, Benolkin K, White T, Luciana M. Affective bias and response modulation following tyrosine depletion in healthy adults. *Neuropsychopharmacology*. 2006;31:2523-2536.
121. Lee S, Lee DK. What is the proper way to apply the multiple comparison test? *Korean J Anesthesiol*. 2018;71:353-360.
122. Larson MJ, Clayton PE, Primosch M, Leyton M, Steffensen SC. The effects of acute dopamine precursor depletion on the cognitive control functions of performance monitoring and conflict processing: an event-related potential (ERP) study. *PLoS one*. 2015;10:e0140770-e0140770.
123. Ramdani C, Vidal F, Dagher A, Carbone L, Hasbroucq T. Dopamine and response selection: an acute phenylalanine/tyrosine depletion study. *Psychopharmacology*. 2018;235:1307-1316.
124. Vidal F, Burle B, Grapperon J, Hasbroucq T. An ERP study of cognitive architecture and the insertion of mental processes: Donders revisited. *Psychophysiology*. 2011;48:1242-1251.
125. Borwick C, Lal R, Lim LW, Stagg CJ, Aquili L. Dopamine depletion effects on cognitive flexibility as modulated by tDCS of the dIPFC. *Brain Stimul*. 2020;13:105-108.
126. Robinson OJ, Standing HR, DeVito EE, Cools R, Sahakian BJ. Dopamine precursor depletion improves punishment prediction during reversal learning in healthy females but not males. *Psychopharmacology (Berl)*. 2010;211:187-195.
127. Cools R, D'Esposito M. Inverted-u-shaped dopamine actions on human working memory and cognitive control. *Biol Psychiatry*. 2011;69:e113-e125.
128. Jongkees BJ, Hommel B, Kühn S, Colzato LS. Effect of tyrosine supplementation on clinical and healthy populations under stress or cognitive demands—A review. *J Psychiatr Res*. 2015;70:50-57.
129. Colzato LS, Jongkees BJ, Sellaro R, van den Wildenberg WPM, Hommel B. Eating to stop: Tyrosine supplementation enhances inhibitory control but not response execution. *Neuropsychologia*. 2014;62:398-402.
130. Stock A-K, Colzato L, Beste C. On the effects of tyrosine supplementation on interference control in a randomized, double-blind placebo-control trial. *Eur Neuropsychopharmacol*. 2018;28:933-944.
131. Steenbergen L, Sellaro R, Hommel B, Colzato LS. Tyrosine promotes cognitive flexibility: Evidence from proactive vs. reactive control during task switching performance. *Neuropsychologia*. 2015;69:50-55.
132. Robson A, Lim LW, Aquili L. Tyrosine negatively affects flexible-like behaviour under cognitively demanding conditions. *J Affect Disord*. 2020;260:329-333.
133. Kvetnansky R, Sabban EL, Palkovits M. Catecholaminergic systems in stress: structural and molecular genetic approaches. *Physiol Rev*. 2009;89:535-606.
134. Colzato LS, Steenbergen L, Sellaro R, Stock A-K, Arning L, Beste C. Effects of l-Tyrosine on working memory and inhibitory control are determined by DRD2 genotypes: a randomized controlled trial. *Cortex*. 2016;82:217-224.
135. Dennison O, Gao J, Lim LW, Stagg CJ, Aquili L. Catecholaminergic modulation of indices of cognitive flexibility: a pharmac-tDCS study. *Brain Stimul*. 2019;12:290-295.
136. Cools R, Robinson OJ, Sahakian B. Acute tryptophan depletion in healthy volunteers enhances punishment prediction but does not affect reward prediction. *Neuropsychopharmacology*. 2008;33:2291-2299.
137. Crockett MJ, Clark L, Apergis-Schoute AM, Morein-Zamir S, Robbins TW. Serotonin modulates the effects of pavlovian aversive predictions on response vigor. *Neuropsychopharmacology*. 2012;37:2244-2252.
138. Crockett MJ, Clark L, Robbins TW. Reconciling the role of serotonin in behavioral inhibition and aversion: acute tryptophan depletion abolishes punishment-induced inhibition in humans. *J Neurosci*. 2009;29:11993-11999.
139. Robinson OJ, Cools R, Sahakian BJ. Tryptophan depletion disinhibits punishment but not reward prediction: implications for resilience. *Psychopharmacology*. 2012;219:599-605.
140. Cools R, Blackwell A, Clark L, Menzies L, Cox S, Robbins TW. Tryptophan depletion disrupts the motivational guidance of goal-directed behavior as a function of trait impulsivity. *Neuropsychopharmacology*. 2005;30:1362-1373.
141. Macoveanu J, Rowe JB, Hornboll B, et al. Playing it safe but losing anyway—Serotonergic signaling of negative outcomes in dorsomedial prefrontal cortex in the context of risk-aversion. *Eur Neuropsychopharmacol*. 2013;23:919-930.
142. Worbe Y, Palminteri S, Savulich G, et al. Valence-dependent influence of serotonin depletion on model-based choice strategy. *Mol Psychiatry*. 2016;21:624-629.
143. Campbell-Meiklejohn D, Wakeley J, Herbert V, et al. Serotonin and Dopamine Play Complementary Roles in Gambling to Recover Losses. *Neuropsychopharmacology*. 2011;36:402-410.
144. Geurts DEM, Huys QJM, den Ouden HEM, Cools R. Serotonin and aversive pavlovian control of instrumental behavior in humans. *J Neurosci*. 2013;33:18932-18939.
145. Hebart MN, Gläscher J. Serotonin and dopamine differentially affect appetitive and aversive general Pavlovian-to-instrumental transfer. *Psychopharmacology*. 2015;232:437-451.
146. Rogers RD, Tunbridge EM, Bhagwagar Z, Drevets WC, Sahakian BJ, Carter CS. Tryptophan depletion alters the decision-making of healthy volunteers through altered processing of reward cues. *Neuropsychopharmacology*. 2003;28:153-162.
147. Anderson IM, Richell RA, Bradshaw CM. The effect of acute tryptophan depletion on probabilistic choice. *J Psychopharmacol*. 2003;17:3-7.
148. Tobia MJ, Guo R, Schwarze U, et al. Neural systems for choice and valuation with counterfactual learning signals. *NeuroImage*. 2014;89:57-69.
149. Neukam PT, Kroemer NB, Deza Araujo YI, et al. Risk-seeking for losses is associated with 5-HTTLPR, but not with transient changes in 5-HT levels. *Psychopharmacology*. 2018;235:2151-2165.
150. Seymour B, Daw ND, Roiser JP, Dayan P, Dolan R. Serotonin selectively modulates reward value in human decision-making. *J Neurosci*. 2012;32:5833-5842.
151. Demoto Y, Demoto Y, Okada G, et al. Neural and personality correlates of individual differences related to the effects of acute tryptophan depletion on future reward evaluation. *Neuropsychobiology*. 2012;65:55-64.
152. Schweighofer N, Bertin M, Shishida K, et al. Low-serotonin levels increase delayed reward discounting in humans. *J Neurosci*. 2008;28:4528-4532.
153. Tanaka SC, Schweighofer N, Asahi S, et al. Serotonin differentially regulates short- and long-term prediction of rewards in the ventral and dorsal striatum. *PLoS one*. 2007;2:e1333.

154. Worbe Y, Savulich G, de Wit S, Fernandez-Egea E, Robbins TW. Tryptophan depletion promotes habitual over goal-directed control of appetitive responding in humans. *Int J Neuropsychopharmacol*. 2015;18:pyv013.
155. Graybiel AM, Grafton ST. The striatum: where skills and habits meet. *Cold Spring Harb Perspect Biol*. 2015;7:a021691.
156. Tanaka SC, Shishida K, Schweighofer N, Okamoto Y, Yamawaki S, Doya K. Serotonin affects association of aversive outcomes to past actions. *J Neurosci*. 2009;29:15669-15674.
157. Gärtner A, Strobel A, Reif A, Lesch K-P, Enge S. Genetic variation in serotonin function impacts on altruistic punishment in the ultimatum game: A longitudinal approach. *Brain Cogn*. 2018;125:37-44.
158. Pearson R, McGeary JE, Beevers CG. Association between serotonin cumulative genetic score and the Behavioral Approach System (BAS): moderation by early life environment. *Pers Individ Dif*. 2014;70:140-144.
159. Leyton M, van der Rot M, Booij L, Baker GB, Young SN, Benkelfat C. Mood-elevating effects of d-amphetamine and incentive salience: the effect of acute dopamine precursor depletion. *J Psychiatry Neurosci*. 2007;32:129-136.
160. Bjork JM, Grant SJ, Chen G, Hommer DW. Dietary tyrosine/phenylalanine depletion effects on behavioral and brain signatures of human motivational processing. *Neuropsychopharmacology*. 2014;39:595-604.
161. Nagano-Saito A, Cisek P, Perna AS, et al. From anticipation to action, the role of dopamine in perceptual decision making: an fMRI-tyrosine depletion study. *J Neurophysiol*. 2012;108:501-512.
162. Frank S, Veit R, Sauer H, et al. Dopamine depletion reduces food-related reward activity independent of BMI. *Neuropsychopharmacology*. 2016;41:1551-1559.
163. Kelm MK, Boettiger CA. Effects of acute dopamine precursor depletion on immediate reward selection bias and working memory depend on catechol-O-methyltransferase genotype. *J Cogn Neurosci*. 2013;25:2061-2071.
164. Lachman HM, Papolos DF, Saito T, Yu Y-M, Szumlanski CL, Weinshilboum RM. Human catechol-O-methyltransferase pharmacogenetics: description of a functional polymorphism and its potential application to neuropsychiatric disorders. *Pharmacogenetics*. 1996;6:243-250.
165. de Wit S, Standing HR, Devito EE, et al. Reliance on habits at the expense of goal-directed control following dopamine precursor depletion. *Psychopharmacology*. 2012;219:621-631.
166. Thirkettle M, Barker L-M, Gallagher T, Nayeb N, Aquila L. Dissociable effects of tryptophan supplementation on negative feedback sensitivity and reversal learning. *Front Behav Neurosc*. 2019;13.