

Eating to stop: Tyrosine supplementation enhances inhibitory control but not response execution



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ABSTRACT

Animal studies and research in humans have shown that the supplementation of tyrosine, or tyrosine-containing diets, increase the plasma tyrosine and enhance brain dopamine (DA). However, the strategy of administering tyrosine (and the role of DA therein) to enhance cognition is unclear and heavily debated. We studied, in a healthy population, whether tyrosine supplementation improves stopping overt responses, a core cognitive-control function. In a double-blind, placebo-controlled, within-subject design, one hour following the administration of tyrosine (corresponding to the beginning of the 1 h-peak of the plasma concentration) or placebo, participants performed a stop-signal task—which taps into response inhibition and response execution speed. Participants in the Tyrosine condition were more efficient in inhibiting unwanted action tendencies but not in reacting to go signals. This is the first demonstration that the supplementation of tyrosine selectively targets, and reliably improves the ability to stop overt responses.

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1. Introduction

Tyrosine is one of the most investigated amino acids, the building blocks of proteins. It is contained in food such as fish, soy, eggs, milk and bananas, and it is the precursor (the chemical that precedes another compound in the biochemical pathway) of the neurochemical dopamine (DA). Animal studies and research in humans have shown that the supplementation of tyrosine, or tyrosine-containing diets, increase the plasma tyrosine and enhance brain DA release, in particular from activated neurons (Acworth, During, & Wurtman, 1988; During, Acworth, & Wurtman, 1988; see Deijen, 2005, for a comprehensive review). Even though the neurobiology of tyrosine supplementation is not yet completely understood, this phenomenon does not seem to be subject to dose-dependent effects (Deijen & Orlebeke, 1994; Shurtleff, Thomas, Schrot, Kowalski, & Harford, 1994). This indicates that the relation between tyrosine and cognitive performance does not follow the inverted U-shaped dose–effect curve that is typical for dopaminergic agonists (Cools, 2006). Once the optimal level is reached, higher levels of tyrosine will thus no

longer increase DA levels, as the enzyme tyrosine hydroxylase, which converts tyrosine into DA, will be inhibited (Gibson & Wurtman, 1977). Therefore, even excessive levels of tyrosine administration are not expected to impair cognitive processes.

Previous literature has mainly focused on the supplementation of tyrosine to reverse conditions associated with dopaminergic-based pathologies, such as Parkinson's disease (Growdon, Melamed, & Logue, 1982; Lemoine, Robelin, Sebert, & Mouret, 1989), phenylketonuria (van Spronsen, van Dijk, & Smit, 1996), depression (Gelenberg, Wojcik, Gibson, & Wurtman, 1983; Gelenberg & Gibson, 1984; Gelenberg, Wojcik, & Falk, 1990) and attention deficit disorder (Wood, Reimherr, & Wender, 1985; Reimherr, Wender, Wood, & Ward, 1987). Furthermore, the role of tyrosine as “counteractor” has been largely investigated under conditions that cause brain DA depletion, such as stress. In humans, tyrosine has been shown to reverse stress-induced deficits in working memory and attentional tasks (Deijen & Orlebeke, 1994; Shurtleff et al., 1994; Mahoney, Castellani, & Kramer, 2007). Only in one study tyrosine has been administered without exposure to stress, revealing beneficial effects, but only when performing more tasks at the same time (Thomas, Lockwood, Sing, & Deuster, 1999). This indicates that tyrosine may reverse “ego-depletion” (Baumeister, Bratslavsky, Muraven, & Tice, 1998) (i.e. reduced self-control after a depleting task), but only when cognitive control is required. This should not be

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surprising given that executive control is considered to emerge from the interplay between the prefrontal cortex (PFC) and the striatum, which both are driven by DA (Cools, 2006)—the precursor of which is tyrosine.

The current study focused, for the first time, on the acute effect of tyrosine supplementation on the inhibition of behavioral responses—a key cognitive control function (Logan & Cowan, 1984; Logan, 1994) that is known to be modulated by DA. Indeed, inhibitory control is enhanced after the acute intake of d-amphetamine and cocaine, drugs that stimulate DA release (Fillmore, Rush, & Abroms, 2005; Fillmore, Rush, & Hays, 2006). Along the same line, Colzato et al. (2007) reported response inhibition (assessed by means of the stop-signal task developed by Logan & Cowan, 1984) to be impaired in chronic recreational users of cocaine (Colzato, van den Wildenberg, & Hommel, 2007), who are likely to suffer from reduced dopamine D2 receptors in the striatum (Volkow, Fowler, & Wang, 1999). Participants pressed a left or right button as soon as a green left- or right-pointing arrow appeared (go trials). However, in some trials the color of the arrow suddenly changed to red, in which case the participants were supposed to refrain from responding (stop trials). This stop-signal task measures both the efficiency of response execution (by means of reaction time to go-signals) and the efficiency in inhibitory control (by means of the stop signal reaction time or SSRT, where longer SSRT reflect general slowing of inhibitory processes and indicate a lower level of inhibitory efficiency). Cocaine users needed significantly more time to inhibit responses to stop-signals than non-users.

Given the role of DA in modulating response inhibition, we expected the supplementation of tyrosine to enhance stopping control. Moreover, based on the ego-depletion hypothesis (Baumeister et al., 1998), we expected this effect to be limited to stopping overt responses without affecting response execution speed. Demanding tasks, such as stopping on time, may deplete the available control resources more than easy tasks, such as reacting to go signals. Accordingly, we assumed tyrosine to be able to replenish the missing resources when more control is needed to carry out the task, as in the case of inhibiting unwanted action tendencies.

2. Experimental procedures

2.1. Participants

Twenty-two healthy female adults (mean age=20.4 years; mean Body Mass Index=21.5) with no cardiac, hepatic, renal, neurological or psychiatric disorders, personal or family history of depression, migraine and medication or drug use participated in the experiment and served in two experimental sessions separated by 3–7 days. A double blind, placebo-controlled, randomized cross-over design with counterbalancing of the order of conditions was used to avoid expectancy effects. Placebo and L-Tyrosine dose corresponded to oral dose (powder) of 2.0 g of microcrystalline cellulose (Sigma-Aldrich Co. LLC) and of 2.0 g of tyrosine (supplied by Bulkpowders Ltd.) dissolved in 400 ml of orange juice. Following Markus, Firk, Gerhardt, Kloek and Smolders (2008), women using contraception were tested when they actually used the contraception pill. On each experimental morning, participants arrived at the laboratory at 9:30 a.m. Participants had been instructed to fast overnight; only water or tea without sugar was permitted. In addition, subjects were not allowed to use any kind of drugs before and during the experiment or to drink alcohol the day before their participation and arrival at the laboratory. Written informed consent was obtained from all subjects; the protocol and the remuneration arrangements of 20 euro were approved by the

local ethical committee (Leiden University, Institute for Psychological Research).

2.2. Apparatus and stimuli

The experiment was controlled by a ACPI uniprocessor PC running on an Intel Celeron 2.8 GHz processor, attached to a Philips 109B6 17 in. monitor (LightFrame 3, 96 dpi with a refresh rate of 120 Hz). Responses were made by pressing the “Z” or “?” of the QWERTY computer keyboard with the left and right index finger, respectively. Participants were required to react quickly and accurately by pressing the left and right key in response to the direction of a left- or right-pointing green arrow (go trials) of about $3.5 \times 2.0 \text{ cm}^2$ with the corresponding index finger.

2.3. Stop-signal task

Each experimental session consisted of a 30-min session in which participants completed a version of the stop-signal task adopted from Colzato et al. (2007), Colzato, van den Wildenberg, van der Does, & Hommel, 2010; Colzato, van den Wildenberg, & Hommel, 2013). Arrows were presented pseudo-randomly for maximal 1500 ms, with the constraint that they signaled left- and right-hand responses equally often. Arrow presentation was response-terminated. Intervals between subsequent go signals varied randomly but equiprobably, from 1250 to 1750 ms in steps of 125 ms. During these interstimulus intervals, a white fixation point (3 mm in diameter) was presented. The green arrow changed to red on 25% of the trials, upon which the choice response had to be aborted (stop trials). A staircase-tracking procedure dynamically adjusted the delay between the onset of the go signal and the onset of the stop signal to control inhibition probability (Levitt, 1971). After a successfully inhibited stop trial, stop-signal delay in the next stop trial increased by 50 ms, whereas the stop-signal delay decreased by 50 ms in the next stop trial when the participant was unable to stop. This algorithm ensured that motor actions were successfully inhibited in about half of the stop trials, which yields accurate estimates of SSRT and compensates for differences in choice RT between participants (Band, van der Molen, & Logan, 2003). Individual SSRTs were calculated according to the *integration method* (see Logan & Cowan, 1984, see Fig. 1). The stop task consisted of five blocks of 104 trials each, the first of which served as a practice block to obtain stable performance.

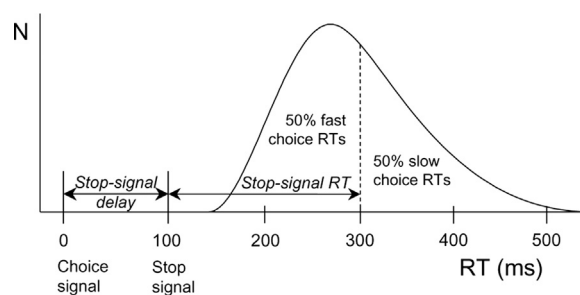


Fig. 1. Calculation of stop-signal RT (SSRT) according to a race model. Following the race model assumption of independence (Logan & Cowan, 1984), the RT distribution of the go process is the same whether or not a stop signal is presented. The left side of the go RT distribution represents fast responses that escape inhibition. The right side represents slow responses that will be inhibited. If participants failed to stop on $n\%$ of the stop trials (here 50%), the finishing time of the stop process was on average equal to the n th percentile of the go RT distribution (here 300 ms). The mean stop signal delay (SSD, 100 ms) was then subtracted from the n th percentile of the go RT distribution, resulting in the estimate of the mean SSRT (200 ms).

2.4. Physiological and mood measurements

Heart rate (HR) and systolic and diastolic blood pressure (SBP and DPB) were measured from the non-dominant arm with a OSZ 3 Automatic Digital Electronic Wrist Blood Pressure Monitor (Speidel and Keller). Mood was rated on a 9 × 9 Pleasure × Arousal grid (Russell, Weis, & Mendelsohn, 1989) with values ranging from -4 to 4.

2.5. Procedure and design

All participants were tested individually. Upon arrival, they were asked to rate their mood and HR, SBP and DPB were collected. One hour following the administration of tyrosine (corresponding to the beginning of the 1 h-peak of the plasma concentration; Glaeser, Melamed, Growdon, & Wurtman, 1979) or placebo, participants rated again their mood before having HR, SBP and DBP measured for the second time. Next, participants were presented with the stop-signal task (Logan & Cowan, 1984). After the behavioral task, participants again rated their mood before having HR, SBP and DBP measured for the third time.

2.6. Statistical analysis

A significance level of $p < 0.05$ was adopted for all statistical tests.

2.6.1. Stop-signal task

Individual SSRTs for stop-signal trials and mean RT to go-signals were calculated to index response inhibition and response execution speed for all participants. Mean SSRTs and mean RT to go-signals were analyzed separately by means of repeated measure ANOVAs with condition (Placebo vs. Tyrosine) as within-subject factor. Additionally, to evaluate the robustness of our results, for both mean SSRTs and mean RTs to go-signals we calculated Bayesian information criteria (BIC) values to estimate a Bayes factor and generate the posterior probability associated with the occurrence of the null (H_0) and alternative (H_1) hypotheses, given the observed data (see Masson, 2011, and Wagenmakers, 2007). This method allows making inferences about both significant and nonsignificant effects by providing the exact probability of their occurrence. Furthermore, to investigate the effect of tyrosine supplementation on post-error slowing, we computed RTs for Go trials that immediately followed a stop-signal trial. More specifically, after having taken into account trial sequence,

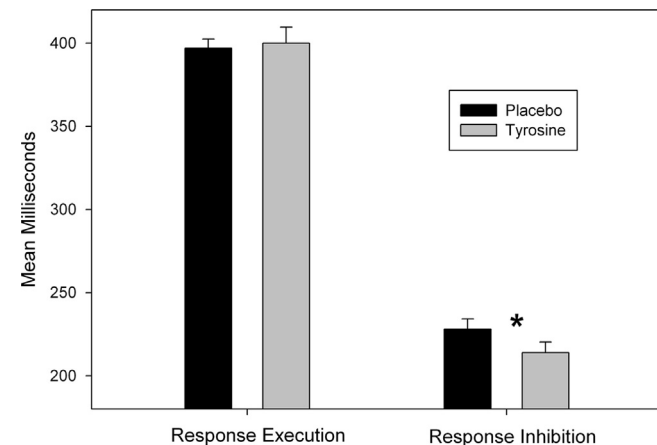


Fig. 2. Mean SSRT (response inhibition) and Mean Go RT (response execution speed) as a function of condition (Placebo vs. Tyrosine). Asterisk indicates significant ($*p < 0.05$) effect of tyrosine on mean SSRT. Vertical capped lines atop bars indicate standard error of the mean.

we split stop-signal trials according to inhibition success by comparing post-stop trial adjustments immediately after a successful stop trial vs. after a failed stop trial. That is, post-stop trials were sorted into mapping repetitions (a stop trial with an arrow pointing to the left is followed by a go trial with an arrow pointing also to the left) vs. alternations (a stop trial with an arrow pointing to the left is followed by a go trial with an arrow pointing to the right). This way we were able to test the effect of stopping success (successful stop vs. failed stop) and arrow repetition (repetition vs. alternation) on RT on the subsequent Go trial.

2.6.2. Physiological and mood measurements

Mood, HR, BPS and BPD were analyzed separately by means of repeated-measures ANOVAs with condition (Placebo vs. Tyrosine) and effect of time (first vs. second vs. third measurement) as within-subjects factor.

3. Results

3.1. Stop-signal task

All participants were able to stop their responses on stop-signal trials successfully in about half of the time a stop signal instructed them to do so (51.8% in the Placebo and 51.6% in the Tyrosine condition), indicating that the dynamic tracking algorithm worked well in both conditions. According to the race model that predicts inhibitory success, the stop process and the go process should run independently (Logan & Cowan, 1984). The race model predicts that the RT derived from stop trials that escaped inhibition (failed-stop RT) is shorter than the mean Go RT. This prediction was confirmed for both the Tyrosine condition and the Placebo condition. On average, failed-stop RT was about 43 ms shorter than mean Go RT, $F(1, 21) = 128.11$, $p < 0.001$, $MSE = 306.77$, $\eta^2 p = 0.859$. The percentage of choice errors to go-signals was low and did not discriminate between Placebo (1.1%) and Tyrosine condition (1.2%). Most importantly, SSRTs were significantly longer in the Placebo (228 ms) than in the Tyrosine condition (214 ms), $F(1, 21) = 5.83$, $p < 0.05$, $MSE = 456.57$, $\eta^2 p = 0.217$, see Fig. 2. The Bayesian probability associated with H_1 was 0.76 which, on the basis of the guidelines proposed by Raftery (1995), represents positive evidence in favor of H_1 (the same probability of H_0 was complementary, i.e., 0.24). Analyses of mean RT to go-signals showed that participants did not react faster in the Placebo (397 ms) than in the Tyrosine condition (401 ms), $F < 1$. Bayesian analysis revealed that, based on our data, the posterior probability of H_0 was 0.81, which represents positive evidence for H_0 (cf. Raftery, 1995). This is consistent with our expectation that tyrosine supplementation would enhance response inhibition while leaving performance relating to response execution unaffected.

This same pattern of results was obtained after controlling for the order in which sessions were administered, $F(1, 20) = 4.58$, $p < 0.045$, $MSE = 304.607$, $\eta^2 p = 0.186$ (SSRTs), and was confirmed

Table 1

Summary statistics of the posterior SSRTs distribution of the group-level mean and standard deviation (SD) parameters for the Placebo and Tyrosine sessions.

SSRT distribution	Placebo	Tyrosine
Parameters estimation		
μ	190	179
SD(μ)	20.6	19.5
σ	22	21
SD(σ)	45.5	45.5
τ	26	31
SD(τ)	54.6	45.1

by additional analyses run separately for the Go RTs and the SSRTs when controlling for the analogous effect on the complementary measure, calculated as the difference in performance between Placebo and Tyrosine sessions: $F < 1$ (Go RTs), and $F(1,20)=5.39$, $p < 0.05$, $MSE=367.124$, $\eta^2p=0.212$ (SSRTs).

To investigate the effect of tyrosine on response inhibition more thoroughly, for both Placebo and Tyrosine sessions we estimated the entire distribution of SSRTs—a procedure that has been found to provide a more detailed description of the differences between two experimental conditions or groups (Heathcote, Popiel, & Mewhort, 1991; Matzke & Wagenmakers, 2009). To this end we used the Bayesian parametric approach (BPA) developed by Matzke, Dolan, Logan, Brown, and Wagenmakers (2013a), which assumes that SSRTs are ex-Gaussian distributed and uses Markov chain Monte Carlo sampling (MCMC; e.g., Gamerman & Lopes, 2006) to obtain posterior distributions for SSRT parameters. In fitting the ex-Gaussian distribution (the convolution of normal and exponential functions), three parameters representing different parts of the curve are obtained: μ and σ corresponding to the mean and standard deviation of the normal component, respectively, and τ , corresponding to both the mean and standard deviation of the exponential component—thus representing the positive skew of the distribution. The BPA was implemented using the BEESTs (Bayesian Ex-Gaussian Estimation of Stop-Signal RT distributions) software developed by Matzke and colleagues (Matzke et al., 2013b; see also Matzke et al., 2013a, for details on the procedure). The BPA was applied to hierarchical stop-signal data after having removed outliers (RT slower and faster than two standard deviations from a participant's mean). For the MCMC sampling, the following values were specified in the input arguments of the software: number of chains=3; samples=36,000; burn-in=12,000; thinning=12; predictions=1000. Results revealed that the difference between Placebo and Tyrosine sessions was mainly captured by the μ component of the ex-Gaussian distribution (see Table 1), thus suggesting that tyrosine influences the latency but not the variability of the SSRTs.

3.2. Post-error slowing

The only significant effect obtained was a main effect of Mapping; Go RT immediately following a stop trial with a repeating arrow was longer compared to trials with alternating arrows, 445 vs. 415 ms, $F(1, 21)=48.50$, $p < 0.001$, $MSE=805.34$, $\eta^2p=0.698$. Go RT adjustments did not depend on stopping success, $F < 1$, and no significant effects of tyrosine were obtained on post-stop adjustments ($F_s < 1$).

3.3. Physiological and mood measurements

ANOVAs revealed that HR (74 vs. 71 vs. 67 and 75 vs. 70 vs. 65 after placebo and tyrosine, respectively), BPD (70 vs. 69 vs. 67 and 69 vs. 68 vs. 68 after placebo and tyrosine), BPS (111 vs. 111 vs. 110 and 115 vs. 113 vs. 109 after placebo and tyrosine), and mood (1.1 vs. 1.5 vs. 1.0 and 1.4 vs. 1.3 vs. 0.9 after placebo and tyrosine) did not significantly change after the intake of tyrosine, $F_s < 1$.

4. Conclusions

This study tested, for the first time, whether the supplementation of tyrosine, the precursor of DA, is associated with a detectable selective enhancement in response inhibition. As expected, in the Tyrosine condition participants were more efficient in inhibiting unwanted action tendencies than in the Placebo condition while response execution was unaffected.

Our results fit with the idea that, in healthy humans, tyrosine works against the phenomenon of “ego-depletion”—the exhaustion

of limited cognitive control resources (Baumeister et al., 1998). Demanding tasks, such as stopping on time, may deplete the available control resources more than easy tasks, such as reacting to go signals. Accordingly, tyrosine may be able to replenish the missing resources when more control is needed to carry out the task.

Our results are also consistent with the idea that DA plays a key role in stopping overt responses. Indeed, a number of patient studies have provided converging evidence for the involvement of DA in response inhibition. Compared to healthy controls, Parkinson's patients, who suffer from loss of dopaminergic cells in the basal ganglia, show difficulties in inhibiting unwanted action tendencies (Guggel, Rieger, & Feghoff, 2004; Wylie, Ridderinkhof, Bashore, & van den Wildenberg, 2010). In line with this picture, Colzato et al., (2010, 2013) reported response inhibition to be predicted by the C957T polymorphism at the DRD2 gene in a young and in aging populations. In contrast, COMT Val58/108Met polymorphism seems to have little if any association with cognitive function (Barnett, Scoriels, & Munafo, 2008, for a recent review). Moreover, very recently, Ghahremani et al. (2012) have found that striatal dopamine D2/D3 receptor availability was negatively correlated with SSRTs and positively correlated with inhibition-related fMRI activation in frontostriatal neural circuitry. Most importantly, correlations involving D2/D3 receptor availability were more robust in the dorsal regions (caudate and putamen) of the striatum, in line with previous findings of striatal activation accompanying stopping (Vink et al., 2005; Aron & Poldrack, 2006; Zandbelt & Vink, 2010). Finally, ADHD patients (see, Alderson, Rapport, & Kofler, 2007, for a recent review) and recreational users of cocaine (Colzato et al., 2007), who are likely to suffer from reduced dopamine D2 receptors in the striatum (Volkow et al., 1999), need significantly more time to inhibit responses to stop-signals than non-users.

The present findings raise the question whether tyrosine supplementation might also enhance other cognitive control functions, such as the “shifting” between tasks and mental sets (also called “flexibility”), and the “updating” (and monitoring of) working memory representations (Miyake et al., 2000). Moreover, it would be very useful to explore the direct effect of prolonged use of tyrosine supplementation on the brain. It remains to be demonstrated, for instance, that tyrosine use produces long-term changes at the neuromodulatory (enhanced functioning of DAD2 receptors) and at functional level (in PFC and striatum) proportionally to the degree of behavioral performance enhancements.

Future research needs also to take individual differences into account. There is ample evidence suggesting a considerable role for individual differences with respect to the efficiency of cognitive control processes and the neurotransmitter systems driving them (Cools, 2006). Furthermore, in healthy humans tyrosine has been shown to reverse stress-induced deficits in working memory and attentional tasks, but in particular in individuals who were most affected by the stressors (Deijen & Orlebeke, 1994; Shurtleff et al., 1994; Mahoney et al., 2007)—suggesting individual differences in the reactivity to tyrosine. It makes sense to assume that preexisting neuro-developmental factors (such as genetic variability related to levels of the neurotransmitter systems) affect the degree to which individuals can benefit from tyrosine supplementation, especially because many of them are arguably tapping into cognitive control processes.

Taken altogether, our results support the materialist approach that “you are what you eat” (Feuerbach, 1862)—the idea that the food one eats has a bearing on one's state of mind. The food we intake may thus act as a cognitive enhancer that modulates the way we think, perceive and react to the physical world. In particular, the supplementation of tyrosine, or tyrosine-containing diets, may promote cognitive enhancement in inexpensive, efficient, and healthy ways.

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