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Tyrosine promotes cognitive flexibility: Evidence from proactive vs. reactive control during task switching performance

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ABSTRACT

Tyrosine (TYR), an amino acid found in various foods, has been shown to increase dopamine (DA) levels in the brain. Recent studies have provided evidence that TYR supplementation can improve facets of cognitive control in situations with high cognitive demands. Here we investigated whether TYR promotes cognitive flexibility, a cognitive-control function that is assumed to be modulated by DA. We tested the effect of TYR on proactive vs. reactive control during task switching performance, which provides a relatively well-established diagnostic of cognitive flexibility. In a double-blind, randomized, placebo-controlled design, 22 healthy adults performed in a task-switching paradigm. Compared to a neutral placebo, TYR promoted cognitive flexibility (i.e. reduced switching costs). This finding supports the idea that TYR can facilitate cognitive flexibility by repleting cognitive resources.

1. Introduction

One of the most investigated amino acids is tyrosine (TYR). TYR is the biochemical precursor of norepinephrine (NE) and dopamine (DA), which are neurotransmitters of the catecholinergic system. Early research has shown that TYR supplementation, or a TYR-rich diet, increases plasma TYR levels in the blood (Glaeser et al., 1979) and enhances DA and NE release in the brain of rats (Sved and Fernstrom, 1981; Gibson et al., 1983; Acworth et al., 1988) and humans (Growdon et al., 1982; Wurtman, 1992; Deijen, 2005, for a review). Once the optimal level of DA is reached, TYR is no longer transformed to DA because tyrosine hydroxylase, the enzyme that converts TYR into DA, is inhibited (Udenfriend, 1966; Weiner et al., 1977). Previous studies on the effect of TYR on cognition focused mainly on deficits in TYR to DA conversion (e.g. phenylketonuria; Pietz et al., 1995; van Spronsen et al., 1996), on the depletion of TYR (Fernstrom and Fernstrom, 1995; Harmer et al., 2001), or on DA-related diseases (e.g. Parkinson's disease; Growdon et al., 1982). In healthy individuals, TYR has often been used to reduce the negative effects of conditions that deplete the brain's dopaminergic resources, such as extreme physical stress. The supply of TYR was found to reduce stress-induced impairments of working memory and attentional tasks, but more so in individuals who were particularly sensitive to the stressors (Deijen and Orlebeke, 1994; Shurtleff et al., 1994; Mahoney et al., 2007).

Only recently, the focus has shifted to the possible beneficial effects of TYR on challenging cognitive performance in the absence of physical stress. Indeed, even without exposure to stress, the supplementation of TYR has been shown to have an acute beneficial effect on challenging task performance thought to be related to DA, such as multitasking (Thomas et al., 1999), the updating and monitoring of working memory (Colzato et al., 2013a), stopping on time (Colzato et al., 2014b), and convergent thinking (Colzato et al. 2014a).

The primary goal of the present study was to examine the effect of TYR on cognitive flexibility, a key cognitive-control function (Miyake et al., 2000). A well-established, reliable indicator of cognitive flexibility is task-switching performance (Monsell, 2003; Miyake et al., 2000). The amount of the time needed to switch between two different tasks can be taken to indicate the efficiency in adapting and restructuring cognitive representations, so that smaller switching costs would reflect a higher level of cognitive flexibility. In this kind of paradigm, the sequence of tasks is often regular and predictable (e.g., AABBAABB…). Accordingly, participants know when to prepare for a task switch, so that the interval between the previous response and the upcoming stimulus (the response-stimulus interval or RSI) represents a preparation interval.

Switching costs in tasks as used in the present study are thought to consist of two major components: a preparatory component and a residual component (e.g., Meiran et al., 2000). In

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switch trials participants can use the preparation interval (if sufficiently long and sufficiently predictable: Rogers and Monsell, 1995) to reconfigure their cognitive task set to meet the demands of the upcoming task. The shorter the interval the less likely this reconfiguration will be completed before the stimulus is presented, which fits with the observation that switching costs (i.e., the increase of reaction time in task-switching trials relative to task-repetition trials) are more pronounced with short than with long RSIs (Rogers and Monsell, 1995). However, when the RSI is long, the preparatory component is nearly eliminated (Meiran, 1996). What remains is the residual component, the component that is resistant to preparation, e.g., because the stimulus triggers the involuntary activation of the previous task set and/or because completely inhibiting the previous set requires the actual activation of the new task set (see Kiesel et al., 2010). In any case, the residual component reflects processes that occur after target onset on switch trials, regardless of the amount of preparation time (e.g., Monsell, 2003).

According to Cools and D'Esposito (2010), DA modulates cognitive flexibility by facilitating the update of information in working memory such as the current task set. Indeed, the DA-D2 receptor agonist bromocriptine was found to reduce switching costs and was accompanied by a drug-induced potentiation of striatal activity in participants with a low-span baseline in working memory capacity (Cools et al., 2007). The hypothesis that dopaminergic pathways are crucial in driving cognitive flexibility clearly predicts a beneficial effect of TYR, which in our design translates into the prediction of reduced switching costs. However, the existence of multiple DA pathways with to some degree opposite and counter-acting impact on performance (e.g., a frontal pathway associated with goal maintenance and focusing, and a nigrostriatal pathway associated with inhibition and flexibility; Cools, 2008; Cools and D' Esposito, 2010; van Schouwenburg, Aarts and Cools, 2010) makes it difficult to predict whether the preparatory component or the residual component or both would be affected. Accordingly, we manipulated the RSI, so that we were able to dissociate possible effects of TYR on these two components. An effect of TYR on the preparatory component would be visible in a particularly strong TYR effect on switching costs when RSI is short, while an effect of TYR on the residual component would be visible in a particularly strong TYR effect on switching costs when RSI is long.

2. Methods

2.1. Participants

Twenty-two undergraduate students of the Leiden University (all females, mean age = 19.3 years, SD = 1.5, range 17–23; mean Body Mass Index = 20.9, SD = 1.5, range 19–23; all right-handed) 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. All participants were selected individually via a phone interview by the same lab-assistant using the Mini International Neuropsychiatric Interview (M.I.N.I.; Sheehan et al., 1998). The M.I.N.I. is a well-established brief diagnostic tool in clinical and pharmacological research that screens for several psychiatric disorders and drug use (Sheehan et al., 1998; Colzato et al., 2009; Colzato and Hommel, 2008). Written informed consent was obtained from all subjects; the protocol and the remuneration arrangements of 20 euro in cash payment were approved by the local ethical committee (Leiden University, Institute for Psychological Research).

A double blind, placebo-controlled, randomized cross-over design with counterbalancing of the order of conditions was used to avoid expectancy effects. Participants were exposed to an oral dose (powder) of 2.0 g of L-Tyrosine (TYR) (supplied by Bulkpowders Ltd.) in the TYR condition and to 2.0 g of microcrystalline cellulose (Sigma-Aldrich Co. LLC), a neutral placebo, in the placebo condition. TYR and placebo doses were dissolved in 400 ml of orange juice and were administered in two different experimental sessions, separated by 3-7 days.

Following Markus et al. (2008) and Colzato et al. (2013b) 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 the experiment or to drink alcohol the day before their participation and arrival at the laboratory. Thirty minutes after the administration of either TYR or the neutral placebo participants were allowed to eat an apple.

2.2. Apparatus, stimuli, and task

The experiment was controlled by a PC attached to a 17-inch monitor with a refresh rate of 100 Hz. The task was modeled after Colzato et al. (2010). Throughout each block, a 10-cm square divided into four quadrants was displayed on the computer screen. On each trial, a character pair was presented in a white uppercase Triplex font in the center of one quadrant. Each pair subtended a visual angle of 1.4° both horizontally and vertically. The next stimulus was displayed clockwise in the next quadrant. One pair of adjacent display positions was assigned to the letter task and the other pair to the digit task, so that the display location served as a task cue, and the task changed predictably every second trial. Depending on the task, the relevant character was either a letter or a digit. The second and irrelevant character was either a member of the other category, so that the response afforded by this character was either congruent or incongruent with the task-relevant response, or was drawn from a set of neutral characters (see Fig. 1).

Consonants were sampled randomly from the set ⟨G, K, M, R⟩ vowels from the set ⟨A, E, I, U⟩, even digits from the set ⟨2, 4, 6, 8⟩, odd digits from the set ⟨3, 5, 7, 9⟩ and neutral characters from the set ⟨#,?,*,%⟩, with the restriction that a character could not be repeated on successive trials. The position of the task-relevant character within a pair was randomly determined on each trial. The participants responded with their left index finger (on the "C" key) to indicate "even" or "consonant" and their right index finger (on the "M" key) to indicate "odd" or "vowel".

The participants received a practice set of 9 switch blocks, each with 16 trials, before entering the experimental phase. This consisted of two sets of 15 blocks, one set for each RSI, each block consisting of 16 trials. The RSI was 150 or 1200 ms, and remained constant for a given set. The order of the RSIs was counterbalanced across participants. The stimulus was displayed until a response was registered.

2.3. Procedure and design

All participants were tested individually. Upon arrival, participants were asked to rate their mood on a 9 × 9 Pleasure × Arousal grid (Russell et al., 1989) with values ranging from –4 to 4. Heart rate (HR) and systolic and diastolic blood pressure (SBP and DPB) were collected from the non-dominant arm with an OSZ 3 Automatic Digital Electronic Wrist Blood Pressure Monitor (Spiedel and Keller). One hour following the administration of TYR (corresponding to the beginning of the 1 h-peak of the plasma concentration; Glaeser et al., 1979) or placebo, participants rated again their mood before having HR, SBP and DBP measured for the second time. Immediately after, participants were asked to

perform the task-switching paradigm measuring cognitive flexibility which took about 30 min. After completing it, participants again rated their mood before having HR, SBP and DBP measured for the third time.

2.4. Statistical analysis

Mood (i.e., pleasure and arousal scores), HR, BPS and BPD were analyzed separately by means of repeated-measures analyses of variance (ANOVAs) with condition (Placebo vs. TYR) and effect of time (first vs. second vs. third measurement) as within-subjects factor. The effect of TYR on cognitive flexibility was assessed by means of $2 \times 2 \times 2$ repeated-measures ANOVAs with condition (Placebo vs. TYR). Task Repetition (i.e., repetition vs. alternation of task) and RSI (150 vs. 1200) as within-subject factors.[1] We adopted a significance level of $p < 0.05$ for all statistical tests.

3. Results

3.1. Task-switching performance

Table 1 provides an overview of the outcomes for reaction times (RTs) and percentage of errors (PEs). RTs revealed a significant main effect of Task Repetition, $F(1,21)=112.63$, $p < 0.001$, $\eta^2p=0.84$; and of RSI, $F(1,21)=19.53$, $p < .001$, $\eta^2p=0.48$. These two main effects were involved in two-way interaction, $F(1,21)=20.67$, $p < 0.001$, $\eta^2p=0.50$, and in a three-way interaction involving condition, $F(1,21)=4.45$, $p=0.047$, $\eta^2p=0.18$.

Fisher LSD post-hoc tests showed that switching costs differed significantly between placebo and TYR for the long RSI, $p=0.009$, SEd (standard error of the mean difference) $=10.24$, 95% CI$=(8.30, 50.90)$, but not for the short RSI, $p=0.927$, SEd$=10.24$, 95% CI$=(-22.25, 20.35)$. Hence, TYR promotes cognitive flexibility (i.e., less switching costs), but only for the long RSI (see Fig. 2 and Table 1).

In the error analysis, a significant main effect of Task Repetition was observed, $F(1,21)=50.99$, $p < 0.001$, $\eta^2p=0.71$, due to fewer errors when the task was repeated than alternated. Condition was not involved in any significant effect, $Fs \leq 2.171$, $ps \geq 0.13$.

3.2. Physiological and mood measurements

Table 2 provides an overview of the outcomes for physiological and mood measurements. ANOVAs showed a main effect of timing only for HR, $F=12.099$, $p < 0.001$, indicating that heart rate decreased with the duration of the experiment (72 vs. 71 vs. 66). However, HR, BPD, BPS, pleasure and arousal, did not significantly change after the intake of TYR, $Fs \leq 2.171$, $ps \geq 0.13$. This suggests that we can rule out an account of our results in terms of physiological and mood changes.

4. Discussion

Our findings show that TYR, the precursor of DA, modulates cognitive flexibility as measured by a task-switching paradigm. Participants showed smaller switching costs after the intake of TYR than of a neutral placebo when the preparation interval to switch was long, but not when it was short. This implies that TYR impacts the residual, but not the preparatory, component of switching costs. An effect on the preparatory component might be due to either the speed of task-set retrieval and implementation, or the efficiency to maintain the prepared task set, or some combination of these processes.[2] TYR might have supported these processes by improving sustained attention. This should have been visible as an effect of TYR on the short RSI (reflecting the preparatory component), which however was not obtained. Even though we need to be careful in interpreting a null effect, the absence of a reliable impact of TYR on the preparatory task-switching component might thus be taken to suggest that TYR has little effect on processes underlying the retrieval, implementation, and maintenance of task sets. As these functions are commonly attributed to the frontal dopaminergic pathway, we speculate that this pathway does not belong to the main targets of TYR-induced increases of DA.

In contrast, the residual component of task-switching costs is likely to reflect the online resolution of conflict induced by inertia

Table 1
Mean reaction times (RTs; in ms), percentage of errors (PEs; in percent), and switching costs (alternation - repetition) for placebo and TYR conditions. Standard errors in parentheses.

Variables (SE)	Placebo		TYR	
SOA	150	1200	150	1200
Repetition				
Reaction times (ms)	699 (23)	664 (21)	684 (25)	657 (19)
Percentage of errors (%)	3.8 (0.6)	3.5 (0.6)	4.1 (0.7)	3.1 (0.6)
Alternation				
Reaction times (ms)	940 (36)	858 (35)	926 (35)	822 (29)
Percentage of errors (%)	8.8 (1.3)	9.1 (1.2)	8.5 (1.3)	8.2 (1.3)
Switching costs				
Reaction times (ms)	241 (25.5)	194 (19.5)*	242 (25.3)	165 (17.1)*
Percentage of errors (%)	5.1 (0.9)	5.6 (0.9)	4.3 (1.0)	5.0 (1.0)

* Significant group difference $p < 0.05$.

[1] We also examined effects of cross-talk (i.e., whether the currently irrelevant, unattended symbol of the two-symbol stimulus compound was related to the task or neutral) and congruency (i.e., whether the currently irrelevant, unattended symbol of the two-symbol stimulus compound was signaling the same response as the relevant symbol or not). The only effect we observed was that participants were faster when the unattended symbol of the two-symbol stimulus compound was neutral (711 ms) than when it was related to the task (811 ms), $F(1,21)=274.60$, $p < 0.001$, $\eta^2p=0.92$. Importantly, neither factor was involved in any interaction involving Condition and/or RSI, $Fs \leq 2.90$, $ps \geq 0.10$, so that they were not considered further.

[2] De Jong et al. (1999) proposed an alternative account of residual switching costs in terms of goal neglect. According to this account, such costs may be due to occasional failures to engage in advance preparation, which lengthen RTs. Thus, one may argue that the smaller switching costs observed in the TYR condition when the preparation interval was long are due to improved sustained attention, and thus, to a reduced incidence of trials that fall in the slowest portion of the RTs distribution. To rule out this possibility, we further examined the data of the long RSI by means of a RT distribution analysis (RT bin analysis; De Jong et al., 1994). For each level of Condition (placebo and TYR) and Task Repetition (repetition vs. alternation of the task), the distribution of correct RTs was rank-ordered into quintiles (20% bins) and

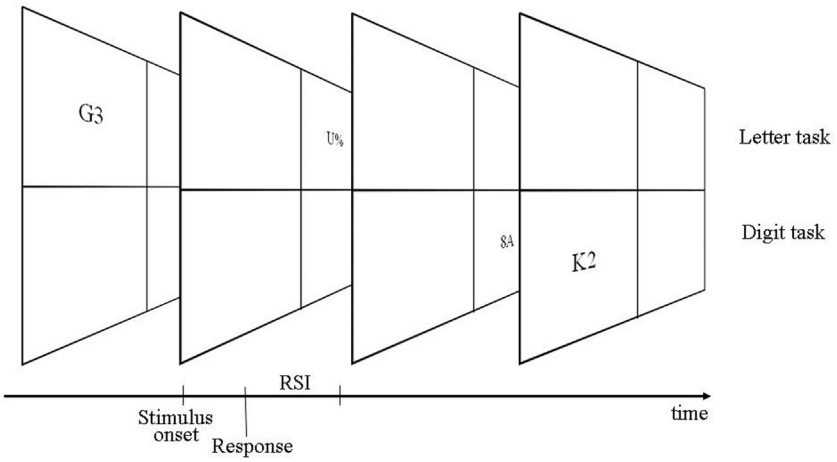

Fig. 1. Illustration of the sequence of events. A stimulus is comprised of two characters, as described in the text. On consecutive trials, stimuli appear in adjacent quadrants rotating clockwise in the four quadrants of the square. One pair of adjacent quadrants is assigned to the letter task (the upper two, in the example), and the other pair to the digit task. As a consequence, the task changes predictably every second trial. The response-stimulus interval (RSI) was either 150 ms or 1200 ms.

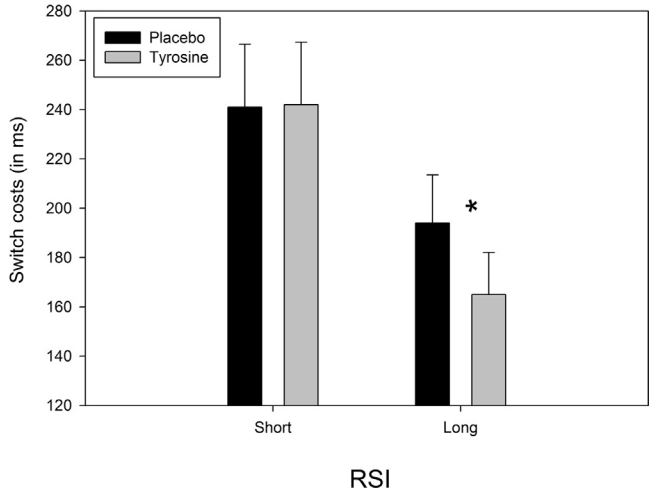

Fig. 2. Mean switching costs (calculated as the RT difference between Task Repetition and Alternation)+SEMs (standard error of the means), as a function of condition (Placebo vs. TYR) and the response-stimulus interval (RSI) (150 and 1200).

Table 2
Mean heart rate values (in beats per minute), systolic and diastolic blood pressure (in mmHg), and pleasure and arousal scores for placebo and TYR conditions. Standard errors in parentheses.

	T1		T2		T3	
	Placebo	*TYR*	*Placebo*	*TYR*	*Placebo*	*TYR*
Heart rate	72 (2)	72 (2)	72 (2)	69 (2)	64 (2)	66 (2)
Systolic blood pressure	114 (2)	112 (3)	115 (3)	112 (3)	113 (3)	109 (2)
Diastolic blood pressure	68 (2)	68 (2)	69 (2)	66 (2)	69 (2)	70 (2)
Pleasure	1.4 (0.3)	1.4 (0.3)	1.6 (0.2)	1.8 (0.2)	1.4 (0.3)	1.4 (0.3)
Arousal	0.4 (0.3)	0.3 (0.4)	0.4 (0.3)	0.6 (0.3)	−0.1 (0.3)	0.1 (0.3)

or stimulus-triggered reactivation of the old task set. The significant effect of TYR on the residual component can thus be taken to reflect TYR-induced support of processes underlying such conflict-resolving processes. Given the available evidence that TYR supplementation has an acute beneficial effect on multitasking (Thomas et al., 1999), the updating and monitoring of working memory (Colzato et al., 2013a), and response inhibition (Colzato et al., 2014b), this might be taken to imply a stronger impact of TYR on the nigrostriatal dopaminergic pathway, which is assumed to be involved in switching to novel information, updating, and inhibition (Cools, 2008; Cools and D'Esposito, 2010; van Schouwenburg, Aarts and Cools, 2010).

Previous neuroimaging studies investigating the effect of preparatory processes and residuals switching costs did not find switch-specific activations in the preparation phase (e.g., Brass and von Cramon, 2002, 2004; Braver et al., 2003; Dove et al., 2000; Luks et al., 2002) but revealed strong activation in the left inferior frontal junction (IFJ) for residual switching costs (Brass and von Cramon, 2004). It is thus possible that TYR supplementation affects the activation of the left IFJ during task switching. Indeed, a direct pharmacological manipulation of DRD2 stimulation has found that fronto-striatal connectivity under bromocriptine was slightly increased for rule switches compared to rule repetitions (Stelzel et al., 2013). Moreover, it would be interesting to know whether TYR affects tonic and/ or phasic DA and the functioning of D1-class vs. D2-class receptors in the striatum, given the important roles of these receptors type in cognitive flexibility.

As suggested by Robbins and Arnsten (2009), there is evidence that noradrenergic coeruleo-cortical projections are involved in different forms of cognitive flexibility, whenever attention must be shifted from one perceptual dimension to another (Birrell and Brown 2000; Dias et al., 1996). Even though TYR is the precursor of both DA and NE, another study from our lab suggests that it was DA that was responsible for our results. In this study, we had participants perform a global-local task-switching paradigm after intake of an oral dose of 80 mg propranolol (a central and peripheral beta-adrenergic antagonist) or placebo in a randomized, double-blind, counterbalanced cross-over design (Steenbergen et al., 2014). We failed to find any significant impact of propanolol on switching costs and congruency effects. One may claim that elevated NE levels resulted in better attention after TYR supplementation, and that this might have improved performance (i.e., less switching costs). However, this consideration is not supported by the observation that the $\alpha 2$ adrenoceptor agonist clonidine (150 μg, oral dose) has no effect on temporal or spatial attention (Nieuwenhuis et al., 2007).

We suggest that TYR administration selectively counteracts DA depletion, a process in which performance levels decline corresponding to the decrease DA function in the brain: When exposed

(*footnote continued*)
submitted to an ANOVA with three within-subjects factors: Condition, Task Repetition and Bin. For both repetition and alternation trials, we did not observe any difference between placebo and TYR in terms of RTs distributions, $F<1$, $p=0.84$.

to physical stress or a cognitively challenging task, the rate of DA synthesis rises (Lehnert et al., 1984; Mahoney et al., 2007). In order to meet the situational demands more DA is synthesized from TYR and L-DOPA. Once these chemical forerunners abate, DA synthesis get sparse, causing less DA availability and accordingly decrements in performance (Muly et al., 1998; Goldman-Rakic et al., 2000). Under these circumstances, TYR may provide the resources necessary to allow DA synthesis to carry on and DA to remain at a level that allows optimal performance (Wurtman et al., 1981). Indeed, TYR supplementation has been found to stimulate DA production in actively firing neurons only (Lenhert et al., 1984; Fernstrom and Fernstrom, 2007). In contrast, when the rate of DA synthesis is low, TYR supplementation amounts to providing unnecessary extra resources from which to synthesize DA, which should not impact DA level or performance.

Taken together, the available observations provide converging evidence for the idea that the amino-acid TYR is a promising cognitive enhancer that facilitates cognitive flexibility.

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