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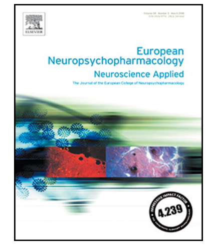

On the effects of tyrosine supplementation on interference control in a randomized, double-blind placebo-control trial

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Abstract
Exerting cognitive control is an effortful endeavor that is strongly modulated by the availability of dopamine (DA) and norepinephrine (NE), which are both synthesized from the amino acid precursor tyrosine. Supplementing tyrosine may increase the synthesis of both catecholamines. This has been suggested to improve executive functioning and potentially even counteract depletion effects in this domain. Yet, it has remained unclear whether tyrosine also improves interference control and whether subliminally and consciously triggered response conflicts are subject to the same modulation.
We investigated this question in a double-blind intra-individual study design. $N = 26$ young healthy subjects performed two consecutive cognitive control tasks that triggered automatic incorrect response tendencies; once with tyrosine supplementation and once with a placebo. The results show that tyrosine decreased the size of consciously perceived conflicts in a Simon Task, but not a Flanker task, thus suggesting that stimulus–response conflicts might be modulated differently from stimulus–stimulus conflicts. At the same time, tyrosine supplementation increased the size of subliminally triggered conflicts whenever a different, consciously perceived

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conflict was also present. This suggests that control-related DA and NE release may increase visuo-motor priming, especially when no conflict-specific top-down control may be triggered to counteract subliminal priming effects. Also, these subliminal conflicts might be aggravated by concurrent control investments in other kinds of conflict. Taken together, our data suggest that beneficial effects of tyrosine supplementation do not require depletion effects, but may be limited to situations where we consciously perceive a conflict and the associated need for conflict-specific control.

1. Introduction

Catecholamines are a class of neurotransmitters that support many important cognitive functions that are indispensable for proper everyday functioning. Dopamine (DA) does not only mediate the effects of reward (Schultz, 2016, 2015) and enable coordinated motor movements (Bowen et al., 1975; Disbrow et al., 2013), but it is also known to modulate executive functions including working memory, inhibition, cognitive flexibility and interference control (Cools, 2016). Norepinephrine (NE), the other main catecholaminergic neurotransmitter, has been shown to modulate attentional processes and facilitate the detection of (rare) distractors as well as support cognitive flexibility, response inhibition, and interference control (Beste et al., 2016; Chamberlain and Robbins, 2013; Chmielewski et al., 2017; Dippel et al., 2017; Mückschel et al., 2017; Sara and Bouret, 2012). While DA and NE are found in distinct neuronal pathways and brain regions, both are formed by enzymatic conversion of the amino acid tyrosine so that changes in (blood) tyrosine levels may potentially alter cognition and behavior known to be modulated by both DA and NE (Deijen, 2005; Jongkees et al., 2015; Luckose et al., 2015). It has already been shown that tyrosine supplementation promotes executive functioning, as it may improve cognitive flexibility (Steenbergen et al., 2015), working memory processes (Colzato et al., 2013) and motor inhibition (Colzato et al., 2014). It has however remained unclear whether tyrosine also helps to resolve conflicts between competing motor responses. Moreover, it is unclear whether tyrosine equally alters consciously and subconsciously triggered response conflicts, as only conflicts that can be consciously detected may trigger effortful cognitive top-down control mechanisms. Given that the detection of conflicts is partly dependent on NE and top-down control is modulated by DA (Chamberlain and Robbins, 2013; Dippel et al., 2017; Mückschel et al., 2017; Sara and Bouret, 2012; Schultz et al., 2015; Schulz et al., 2012; Shenhav et al., 2017; Westbrook and Braver, 2016), it could be speculated that consciously perceived conflicts are more strongly modulated by tyrosine supplementation than subliminal ones.

In the context of competing motor responses, DA and NE might also modulate the detection and processing of task-irrelevant information. Specifically, NE has been shown to play an important role in the detection of deviant stimuli (Chamberlain and Robbins, 2013; Dippel et al., 2017; Mückschel et al., 2017; Sara and Bouret, 2012) and might thus increase processing of task-irrelevant information / distractor stimuli. DA plays a key role in automatic visuomotor priming (Falkenstein et al., 2006; Praamstra and Plat, 2001) and higher DA levels have been associated with increased priming effects (Fluchère et al., 2014; Onur et al., 2011; Wylie et al., 2012) so that DA might increase the size of response conflicts. Such potentially detrimental effects of tyrosine supplementation may be more likely to be found in case of subliminal conflicts, because those conflicts cannot trigger effortful cognitive top-down control mechanisms in the same fashion as consciously perceived conflicts.

Lastly, several studies have claimed that beneficial effects of tyrosine supplementation are often only observed in situations where DA and NE levels are low due to tyrosine deficits and / or previous depletion of catecholamines (Jongkees et al., 2015; Luckose et al., 2015). It is well-known that exerting top-down cognitive control is perceived as effortful due to opportunity costs (i.e. the costs of performing the task as well as the costs of missing out on other options, including the option of not performing the task at all) (Kurzban et al., 2013). It has also been argued that control becomes more costly the longer it is carried out, which is thought to be due to an intrinsic "disutility" of cognitive control (Kool and Botvinick, 2013). In this context, it has been suggested that the increasing cost of continuously exerted control might produce or mimic depletion effects, which have previously often been attributed to a lack of dopamine (Baumeister et al., 2007; Kool and Botvinick, 2014). Yet, DA should play a key role for continuous exertion of control irrespective of the proposed mechanism of depletion. The reason is that DA is not only a key factor in keeping up effortful cognitive control (Shenhav et al., 2017; Westbrook and Braver, 2016), but also conveys utility (Schultz et al., 2015, 2017), including the value of control (Westbrook and Braver, 2016). This means that irrespective of whether continued exertion of cognitive control really depletes DA resources (there is still a rather profound lack of direct evidence for this) or whether increases in disutility demand higher DA levels, increases in DA synthesis should be beneficial and help to keep up cognitive control in either case. This is also in line with studies showing that catecholamine synthesis seems to be increased in case of cognitively challenging tasks (Jongkees et al., 2015; Kvetnansky et al., 2009; Mahoney et al., 2007). It further matches the finding that there are more beneficial effects of tyrosine supplementation in case DA levels are genetically low (Colzato et al., 2016). Taken together, this suggests that the modulatory effects of tyrosine supplementation are perhaps more likely to be found after continuous exertion of cognitive control. Further complementing this, it has been noted that activity within the locus coeruleus (LC) as well as other parts of the NE system plays an important role in keeping up

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