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Review article

# Tryptophan supplementation modulates social behavior: A review

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ABSTRACT

Tryptophan (TRP), the precursor of serotonin (5-HT), is one of the most investigated amino-acids. TRP supplementation can increase 5-HT levels in the brain and for this reason numerous studies have investigated whether administration of TRP can positively influence social behavior that relies on serotonergic function. Here we review the available studies on TRP, to clarify if and under what circumstances TRP supplementation might modulate social behavior. TRP supplementation seems to improve control over social behavior in patients and individuals suffering from disorders or behaviors associated with dysfunctions in serotonergic functioning. In contrast, in healthy humans TRP supplementation seems to promote social behavior. Although more research is needed to disentangle and understand the relations between individual differences, TRP effectivity, 5-HT functioning, social interactions, and context, we conclude TRP can be a promising tool for modulating social behavior.



**Contents**



## 1. Introduction

Social interactions pervade our daily lives. Although 'social behavior' is a very broad term encompassing many different actions, one can distinguish between two major, albeit non-exhaustive categories: on the one hand there is prosocial behavior, which has been defined as voluntary acts intended to help or benefit others, for example by helping or donating (Bar-Tal, 1976; Staub, 1978; Eisenberg, 1982; Brief and Motowidlo, 1986; Penner et al., 2005). On the other hand there is antisocial behavior, which has been defined as voluntary acts intended to harm or disadvantage others, for example through aggression and dysfunctional impulsivity (e.g. Kavussanu et al., 2006; Sage et al., 2006). A different way of classifying social behavior uses the interpersonal circle model of behavior (Moskowitz, 1994, 2010), according to which behavior can be classified along two dimensions, namely agreeable-quarrelsome and dominant-submissive. The dimension of agreeableness and quarrelsomeness bears resemblance to prosocial and antisocial behavior, with prosocial and agreeable behavior typically serving to affiliate with others, whereas antisocial and quarrelsome behavior typically serves to distance the person from others. Notably, neither behavior is exclusively 'dominant' or 'submissive', which comprises an orthogonal dimension.

Interestingly, increased serotonin (5-HT) levels in the brain have been linked to social behaviors such as affiliation and coopera-

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tion (for reviews see Crockett, 2009; Kiser et al., 2012). In contrast, research has shown social behaviors such as aggression and irritability, as well as certain disorders, are related to disturbances in serotonergic functioning, although the GABA-ergic, dopaminergic and glutaminergic systems may be involved as well (Williams et al., 2013; Selvaraj et al., 2014; Lesch et al., 2012; for reviews see Young and Leyton, 2002; Miczek et al., 2002; Kiser et al., 2012). For example, 5-HT dysfunctions have been found to be associated with antisocial, impulsive, and violent criminal behaviors (Brown et al., 1979; Virkkunen and Närvänen 1987; Virkkunen et al., 1994; Liao et al., 2004; Coccaro et al., 2015).

Given this association between 5-HT function and social behavior, there is the possibility that modulating 5-HT could lead to positive changes in social behavior. One method of modulating 5-HT is administering its precursor tryptophan (TRP). TRP is an essential amino-acid that is derived from the diet, as the human body cannot produce TRP itself. Importantly, TRP contributes to brain protein synthesis and can increase 5-HT synthesis in rats (Yuwiler, 1973) and humans (Bowers, 1970; Eccleston et al., 1970). For this reason, numerous studies have investigated whether administration of TRP can positively influence social behavior that relies on serotonergic function (Crockett, 2009; Kiser et al., 2012).

However, findings from TRP studies have not been completely unequivocal and numerous factors – such as individual differences and social context – might determine the effect of TRP on social behavior. In this review, we will summarize the available studies on TRP and social behavior with the aim of illustrating equivocal findings, and, where possible, highlight consensus among studies. Afterwards, we list potential modulators of response to TRP supplementation. In doing so, we hope the present review may stimulate future studies to take into consideration the unresolved inconsistencies as well as the possible modulating factors when designing and analyzing experiments involving TRP. Before reviewing any studies, we will first elaborate on how TRP supplementation influences 5-HT function.

### 1.1. Mechanism of action

After ingesting TRP, its plasma levels increase (Yuwiler et al., 1981) and the synthesis of 5-HT in the brain can be doubled (Young and Gauthier, 1981). Effects of TRP on 5-HT synthesis mainly occur because of the enzyme tryptophan-hydroxylase (TPH), involved in the first step of TRP to 5-HT conversion and responsible for regulating the rate at which TRP is transformed into 5-HT (Young and Gauthier, 1981; Sheehan et al., 1996; Silber and Schmitt, 2010). TPH is already saturated at a dose of 3 g of TRP, which results in doubling of the rate of 5-HT synthesis (Young and Gauthier, 1981). However, lower doses are used as well, which presumably do not fully saturate TPH and therefore increase but not necessarily double 5-HT synthesis (Young and Gauthier, 1981; Sheehan et al., 1996).

In contrast to other large neutral amino-acids (LNAAs) such as valine, leucine, tyrosine, isoleucine, and phenylalanine, TRP is the amino-acid that is least found in protein (Wu, 2009). Thus a diet rich in protein will lead to smaller increases in TRP plasma levels than in the plasma levels of other LNAAs (for a detailed explanation see Le Floc'h et al., 2011). Furthermore, all LNAAs have to be transported through the blood brain barrier (BBB) by the same transport system. As such, the LNAAs compete for transport across the BBB, which limits uptake of TRP in the brain (Oldendorf and Szabo, 1976; Fernstrom, 1990, 2013). As a result of this, brain TRP and 5-HT levels could actually decline when TRP is consumed along with other LNAAs (Fernstrom and Faller, 1978, see also Fig. 1). The intake of pure TRP, however, leads to a significant increase in plasma TRP levels and the TRP:LNAA ratio at approximately 60 min after administration. Peak plasma and TRP:LNAA levels are reached 2 h after intake and remain elevated for at least 7–12 h (Yuwiler et al., 1981; Volavka et al., 1990; Markus et al., 2008).

As reported by Hiratsuka et al. (2013), doses up to 5 g of TRP per day do not cause any known adverse metabolic effects. One study reported side-effects of TRP intake such as dizziness and epigastric pain when administering doses of 3 g daily for 3 weeks, although these complaints were also observed before the start and during the run-in placebo week of the study (Thomson et al., 1982). In a study in which 3 g TRP daily was administered to participants for 12 weeks, one patient reported diarrhea as a side-effect of TRP intake (Van Praag et al., 1972). These studies are two examples of cases in which long-term use of moderate doses of TRP resulted in side-effects. The aforementioned side-effects are more likely to occur when higher doses are used (i.e. 70–200 mg/kg; for a review see Fernstrom, 2012). The number and variety of reported side-effects increases when looking at higher doses taken over longer periods (e.g. 6 g daily for 3 months; Steinberg et al., 1999). Such high doses might not be recommendable not only because of such side-effects, but also because the TPH enzyme is likely to already be saturated by a dose of TRP up to 3 g (Young and Gauthier, 1981), suggesting doses higher than this are unlikely to provide further enhancement of 5-HT function. Lastly, side-effects may occur when TRP is taken in combination with a drug that also enhances 5-HT functioning (e.g. certain antidepressants). These side-effects include tremor, nausea, drowsiness, and dizziness (Fernstrom, 2012). In rare cases, serotonergic functioning can be stimulated too much (e.g. when combining TRP with 5-HT drugs) and "serotonin syndrome" occurs. Symptoms of this syndrome include delirium, myoclonus, hyperthermia, and coma (Fernstrom, 2012).

Regarding the cognitive mechanism underlying effects of TRP on social behavior, a prevalent hypothesis is that TRP - through its effect on the serotonergic system - might bias processing of emotional information. Low 5-HT function has been associated with an increase in aversive processing (Cools et al., 2008a), that is, low 5-HT levels are related to a bias in attention towards punishment (Chamberlain et al., 2006; Cools et al., 2008b) and distractors with a negative emotional load (Murphy et al., 2002), and away from happy facial expressions (Murphy et al., 2002). Conversely, enhanced 5-HT levels - achieved via repeated administration of the selective serotonin reuptake inhibitor (SSRI) citalopram or TRP supplementation - are associated with reduced fear recognition (Harmer et al., 2006) and intensity rating (Gibson et al., 2014), increased recognition of happy faces (Murphy et al., 2006) and intensity rating (Gibson et al., 2014), and reduced attentional vigilance towards negative words (Murphy et al., 2006). However, not every study has demonstrated a selective bias towards positive information with high 5-HT levels and towards negative information with low 5-HT levels. For example, Attenburrow et al. (2003) showed intake of TRP increased the recognition of both happiness and fear. Nevertheless it is clear from these studies that the serotonergic system is closely related to the processing of emotional information. Indeed, Harmer (2008) and Harmer et al. (2009) suggested that decreasing TRP levels may decrease 5-HT synthesis and turnover, resulting in a negative bias in automatic processing of information. Such a bias could potentially promote negative social behaviors like aggression. In contrast, TRP supplementation, similar to antidepressants that raise 5-HT levels (Harmer, 2008), might cause 'positive re-biasing in information processing', resulting in more attentiveness to positive stimuli. It is possible such a bias could promote more positive social behaviors such as affiliation and cooperation.

## 2. Literature overview

Previous reviews have extensively focused on the effect of TRP *depletion* on cognitive functions (Mendelsohn et al., 2009), mood,

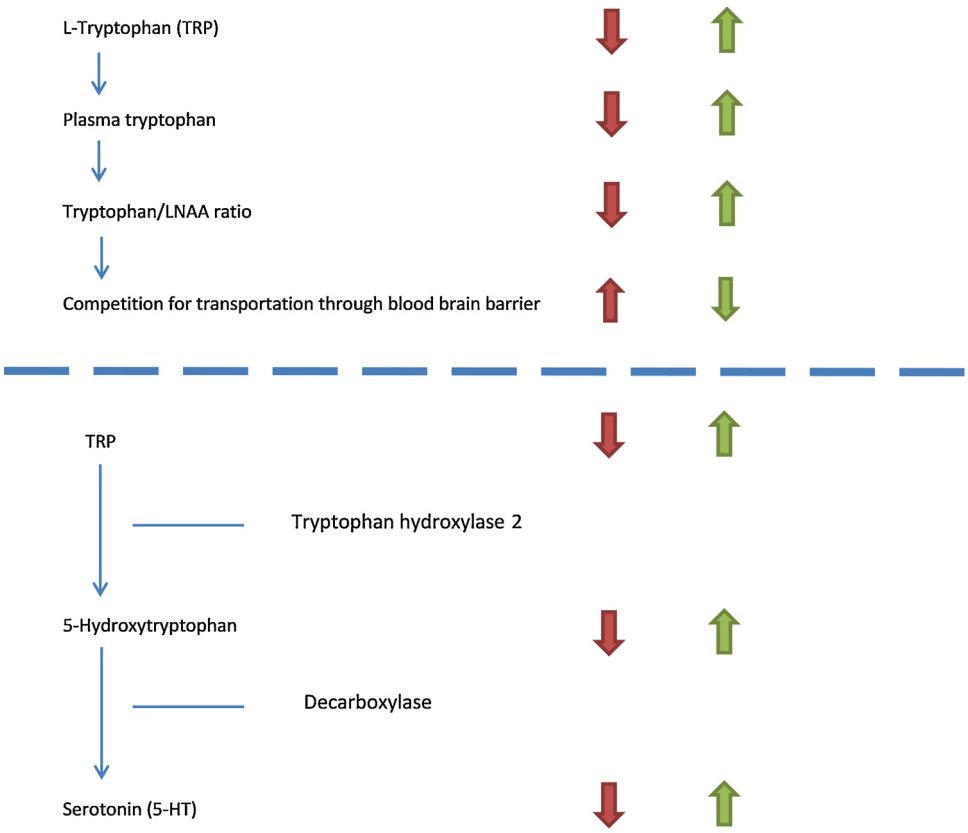


**Fig. 1.** Schematic representation of the effect of acute tryptophan (TRP) depletion (red arrows) and supplementation (green arrows) on TRP to serotonin (5-HT) conversion. Processes above the dashed line take place before travelling through the blood brain barrier, processes below the dashed line after transportation through the blood brain barrier. LNAA = large neutral amino-acids. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

and social behavior (Ruhé et al., 2007; Young and Leyton, 2002; Young, 2013). The general finding in these reviews is that low 5-HT can decrease mood and increase aggressive and antisocial behavior, although results are still equivocal and vary somewhat between studies. In contrast, the goal of the current paper is to review studies on TRP *supplementation* and its effects on social behavior.

Studies reviewed here were found using the keywords "tryptophan"; "supplementation OR loading"; "social" and "behavior" in Web of Science. In addition; forward and backward citations were studied to look for additional studies not directly found through Web of Science. Studies selected for this review had to be studies in humans including at least one TRP supplementation condition and measuring social behavior outcomes.

The available studies on TRP supplementation can be divided into two major domains of research. One line of research has focused on humans with psychiatric disorders and/or showing antisocial behaviors associated with decreased or dysfunctional 5-HT availability in the brain (hereafter, referred to as "clinical populations"). Results of these studies suggest that TRP can serve as a potential treatment or supplement to treatment for clinical symptoms associated with suboptimal or dysregulated 5-HT levels, e.g. in order to promote inhibition of antisocial behavior such as aggression, impulsivity, etc. A different line of research has focused on healthy humans with supposedly normal 5-HT levels. These studies suggest that TRP has promising potential for promoting social behavior, in particular prosocial and agreeable behavior. These two lines of research are used to structure our overview. We start with studies on TRP and clinical populations, followed by studies on healthy individuals. Characteristics and main outcomes of the reviewed studies are presented in Table 1.

### 2.1. Clinical populations: inhibiting antisocial behavior

Many clinical conditions are associated with reduced or dysfunctional 5-HT levels. Hence, it is reasonable to assume that TRP supplementation may improve certain clinical symptoms by altering 5-HT availability. One of the most prominent disorders related to decreased 5-HT functioning is depression (Coppen, 1967; Albert et al., 2012). Indeed, in addition to increasing the effectiveness of antidepressants such as monoamine oxidase inhibitors and tricyclic antidepressants (for a review see Young, 1991), TRP may be effective as an antidepressant alone (for reviews see Shaw et al., 2002; Silber and Schmitt, 2010). However, as pointed out by Silber and Schmitt (2010), the variance between the available studies with regard to dosage, study design, sample size, and sample population makes that there is still little consensus in terms of the effectiveness of TRP in treating depression. For example, TRP has no additional effectiveness when compared to placebo in severely depressed patients (Chouinard et al., 1983; Shaw et al., 2002), but does have positive effects in mild to moderately depressed patients (Thomson et al., 1982; Shaw et al., 2002). Despite the strong connection between depression and social behavior (e.g. Leader and Klein, 1996; Bosc, 2000), to the best of our knowledge, no studies have addressed whether and to what extent TRP supplementation can affect social behavior in depressed patients. However, a study by Hogenelst et al. (2015) did address the idea that TRP supplementation may be beneficial for individuals at risk of developing depression, such as those who have a family history of depression, whose social functioning is altered relative to control individuals (Watters et al., 2013; Mannie et al., 2007). Importantly, Mannie et al. (2007) suggested decreased social functioning, as observed in

**Table 1**
Overview of studies on the effect of tryptophan supplementation on antisocial and prosocial behavior. When available, the mean age is reported alongside the range. TRP = Tryptophan, LNAA = Large neutral amino acids * = study directly measuring social behavior as opposed to indirect measures such as self-reports or questionnaires.

| Authors and year | Design | Sample | Supplement | Dose | Measurement | Psychological outcome | Physiological outcome |
|---|---|---|---|---|---|---|---|
| Hogenelst et al. (2015) | Double blind, placebo controlled, counterbal-anced cross-over, 7-day wash-out period | N = 40 (27 female), mean age 31.5 | L-Tryptophan | 1 g 3 times a day for 14 days | Self-reports | Increased quarrelsomeness (at home), trend to lower agreeableness (at home), decreased negative affect. Placebo first: increased positive affect, decrease in negative cognitions | n/a |
| Moskowitz et al. (2011) | Double blind, placebo controlled, cross-over | Study 1: N = 98 (48 female) Study 2 (individuals selected for high irritability): N = 39 (19 female) | Tryptophan | 1 g 3 times a day for 9 days | Self-reports | Study 1: no effect on spin Study 2: reduction in spin in low agreeable subjects | n/a |
| Morand et al. (1983) | Double blind, placebo controlled, cross-over, 1 week wash-out | N = 12 male schizophrenic patients convicted for person-related crimes, mean age 30.0 | Tryptophan | N = 6: 4 g vs. N = 6: 8 g daily for 4 weeks | Self-reports and reports by ward staff | 4 g: 15% reduction in depressive symptoms, 10% reduction in hostility, 8 g: measures not possible, overall: 30% reduction in incidents when on tryptophan | n/a |
| Volavka et al. (1990) | Double blind, placebo controlled, between-subject, including 1 month baseline observation | N = 20 (8 female) psychiatric inpatients aged 19-56 | 10 g chocolate bars containing 0.5 g tryptophan | 6 g for 3 weeks | Reports by ward staff and biochemical analyses | No effect on aggressive incidents but reduction in need for injections of antipsychotics and sedatives | Increase in TRP:LNAA ratio 2 hours after administration |
| *Bjork et al. (2000) | Double blind, within subject, latin squared (T-, T+, food restricted) including baseline | N = 12 agrressive (mean age 27.9) and 12 non-aggressive men (mean age 31.1) | Amino acid drink with tryptophan | 10.3 g of tryptophan added to a drink containing 15 amino acids | Computer tasks, self-reports and biochemical measures | Decreased aggressive responding in aggressive men, but a trend towards increased aggressive responding in non-aggressive men | Higher plasma free tryptophan in non-aggressive men after ingestion of tryptophan |
| Finn et al. (1998) | Double blind, between-subject, including baseline | N = 48 males, mean age 21.9 | Amino acid drink with tryptophan | 2.3 g of tryptophan added to 100 g LNAAs, acute | Self-reports, biochemical measures | Significant negative correlation between TRP plasma levels and hostile mood. Stronger association between changes in plasma tryptophan and changes in hostility in subjects with high levels of pre-existing hostile traits compared with low levels of hostile traits, and in subjects with high vs. low antisocial traits. | Increase in plasma tryptophan |

Table 1 (*Continued*)

| Authors and year | Design | Sample | Supplement | Dose | Measurement | Psychological outcome | Physiological outcome |
|---|---|---|---|---|---|---|---|
| *Pihl et al. (1995) | Double blind, between-subject | N = 90 males aged 18–34, mean age 24.0 | Amino acid drink with tryptophan | 2.3 vs. 10.3 g of tryptophan added to 100 g of amino acids, acute | Computer tasks, biochemical measures of alcohol | 10.3 g: Lower shock intensity compared to tryptophan depletion | n/a |
| *Cleare and Bond (1995) | Double blind, between-subject, including baseline | N = 24 males high trait aggression, mean age 32.0, N = 24 males low trait aggression, mean age 33.0 | Amino acid drink with tryptophan | 10.3 g of tryptophan added to 100 g of amino acids, acute | Computer tasks, self-reports, physiological measures and biochemical measures | No effects on behavioural task. High trait aggression: decrease in aggressiveness on angry-peaceful, quarrelsome-affable, hostile-friendly and annoyed-composed variables. Low trait aggression: increased drowsiness | Mean plasma tryptophan increase of 1100%, whole blood serotonin rose from 83.7 to 88.2 mcg/1, no effects on skin conductance |
| *Marsh et al. (2002) | Double blind, within subject, counterbal-anced (T− and T +) with fasting control day at the end. | N = 12 females aged 18–36, mean age 26.2 | Amino acid drink with tryptophan | 2.3 g of tryptophan added to 100gr LNAAs, acute | Computer tasks, self-reports and biochemical measures | Decreased aggressive responding | 209% increase in plasma tryptophan |
| *Smith et al. (1986) | Double blind, between-subject | N = 36 males aged 18-25 | Amino acid drink with tryptophan | 2.3 vs. 10.3 g of tryptophan added to 100 g of amino acids, acute | Computer tasks, biochemical measures | No effects on aggression (shock duration and intensity) | 10.3 g goup showed a 1570% increase in free and a 580% increase in total plasma tryptophan, 2.3 g goup showed a 180% increase in free and a 170% increase in total plasma tryptophan |
| *Bjork et al. (1999) | Double blind, within subject, latin squared (T−, T+, food restricted) including baseline | N = 8 males, mean age 32.6 | Amino acid drink with tryptophan | 10.3 g of tryptophan added to a drink containing 15 amino acids | Computer tasks | No significant effects of tryptophan administration on aggressive responding in high-provocation situations | n/a |
| *Nantel-Vivier et al. (2011) | Double blind, placebo controlled, between-subject | N = 23 males aged 10 | Chocolate milkshake containing tryptophan | 500 mg acute | Computer tasks | Decreased decision time during high provocation, optimal responding as function of the level of provocation. Trend towards less impulsiveness, increased perspective taking and better distinction of happiness and fear | n/a |

Table 1 (*Continued*)

| Authors and year | Design | Sample | Supplement | Dose | Measurement | Psychological outcome | Physiological outcome |
|---|---|---|---|---|---|---|---|
| Nemzer et al. (1986) | Double blind, placebo controlled, latin-square cross-over (tryptophan vs. tyrosine vs. d-amphetamine vs. placebo), including baseline measures | N = 14 (3 female) aged 7–12, mean age 9.4 | Tryptophan | 100 mg/kg daily for 1 week | Teacher and parent reports and biochemical analyses | Improvement in parent ratings of impulsivity and concentration | Increase in TRP serum levels |
| aan het Rot et al. (2006) | Double blind, placebo controlled, counterbal-anced cross-over, 6-day wash-out period | N (selected for high quarrelsome-ness) = 39 (19 female), mean age 32.1 | L-Tryptophan | 1 g 3 times a day for 15 days | Self-reports | Decrease in quarrelsome behavior, increase in perceived dominance, agreeableness (men only) and dominance (men only). Only when placebo first: Increase in pleasantness of, and positive, affect, perceived agreeableness. | n/a |
| Moskowitz et al. (2001) | Double blind, placebo controlled, counterbal-anced cross-over, 2-day wash-out period | N = 98 (48 female) aged 18–67 | Tryptophan | 1 g 3 times a day for 12 days | Self-reports | Increased dominance, decreased arousal (females only). Only when placebo first: Decreased quarrelsomeness | n/a |
| *Cerit et al. (2015) | Double blind, placebo controlled, between-subject, pre- and post-intervention assessment | N = 47 (23 female) aged 18–35, mean age 20.3 | Tryptophan | 2.8 g per day for 6 days | Self-reports and computer tasks | Increased rejection of very unfair offers | n/a |
| *Colzato et al. (2013) | Double blind, placebo controlled, between-subject | N = 40 (36 female), mean age 19.4 | Tryptophan | 800 mg acute | Self-reports, computer task and physiological measures | Increase in money transferred to recipient | Decrease in heart rate |
| *Steenbergen et al. (2014) | Double blind, placebo controlled, between-subject | N = 32 (28 female), mean age 21.8 | Tryptophan | 800 mg acute | Self-reports, donating and physiological measures | Increase in money donated to charity | No changes |

these individuals, may be a result of impairments in the processing of emotional stimuli. This is in line with the idea that decreased 5-HT functioning may lead to a negative bias in information processing (Cools et al., 2008a,b) and that antidepressants that raise 5-HT levels cause a re-biasing towards positive information processing (Harmer, 2008). Following this idea, Hogenelst et al. (2015) conducted a double-blind study to investigate whether individuals with a family history of depression would show more agreeable and less quarrelsome behavior after a TRP supplementation intervention (1 g of TRP or placebo, 3 times a day, for 14 days). In contrast to the expectations, however, the intervention had the opposite effect: TRP supplementation led to increased quarrelsome behavior and diminished agreeable behavior. Notably, the findings of Hogenelst et al. (2015) only applied to interactions at home and, as such, it is not clear whether these results generalize to other social contexts. Furthermore, quarrelsomeness is sometimes regarded as a mild form of reactive aggression (Moskowitz, 2010) that, at least in animals, is aimed at enhancing social status, coherence and territorial control and is positively related to serotonergic activity (de Boer et al., 2009). Hence, the authors speculated the increase in quarrelsome behavior may indicate achieving more control over social interactions at home (Hogenelst et al., 2015), instead of promoting social behavior per se. Consistent with the idea that TRP may improve control over social interactions, Moskowitz et al. (2011) found 1 g of TRP taken 3 times a day to lower interpersonal spin (i.e., the large fluctuation in interpersonal behaviors around the interpersonal circumplex across situations) and, thus, to increase social behavior consistency, in individuals with elevated trait irri-

tability and low trait agreeableness. This suggests that individuals with high propensity to anger and/or problems with bonding with others because of their difficulties with the control of interpersonal behavior might benefit from TRP supplementation.

Another prominent psychiatric disorder that has been associated with reduced 5-HT levels is schizophrenia (Meltzer et al., 2003). A study on treating patients with schizophrenia by supplementing them with TRP dates back several decades ago (Morand et al., 1983). This treatment was reported to help reduce the frequency of aggressive incidents in schizophrenic patients convicted for interpersonal crimes (Morand et al., 1983). Another study on female patients showed that TRP (6 g per day) did not affect the frequency of occurrence of aggressive or violent incidents, however it did significantly reduce the need for antipsychotic or sedative injections to control their aggression (Volavka et al., 1990).

Other studies have addressed the role of 5-HT functioning in modulating aggressive, violent, and criminal behaviors, which have previously been associated with 5-HT dysfunctions and reduced 5-HT levels (e.g. Kruesi et al., 1992; Brown et al., 1979; Virkkunen and Närvänen, 1987; Virkkunen et al., 1994; Liao et al., 2004; Coccaro et al., 2015). Given that TRP can enhance 5-HT functioning, TRP might have a positive influence on these antisocial behaviors. Indeed, Bjork et al. (2000) showed that in aggressive men, after TRP supplementation (10.3 g TRP added to an amino acid drink) higher plasma TRP levels were associated with less aggressive responses to provocation as assessed by a modified version of the point subtraction aggression paradigm (Cherek et al., 1996). In a study by Finn et al. (1998), it was found that changes in plasma TRP levels as a result of TRP administration (2.3 g of TRP added to 100 gr of other LNAAs) negatively correlated with hostile mood: increase in TRP levels was associated with less hostility, whereas TRP level reduction was associated with higher hostility. Interestingly, these correlations were found to be stronger for males with high trait levels of hostility and aggression. Further evidence that TRP availability can affect aggressive responses comes from a study by Pihl et al. (1995). In this study aggressive behavior was indexed via the intensity of the shocks people were willing to deliver to another individual after having received themselves shocks with intensities either below their pain threshold (i.e., low provocation condition) or above it (i.e., high provocation condition). It was found that an increase in TRP levels led participants to reduce the intensity of the shocks delivered to the alleged partner. However, such an outcome was only observed for the low provocation condition and when TRP depletion was compared to TRP administration (10.3 g added to 100 g of LNAAs) but not when compared to a balanced drink (2.3 g TRP added to 100 g LNAAs). In another study, TRP supplementation (10.3 g added to 100 g of amino-acids) was found to reduce self-report ratings of angriness, quarrelsomeness, hostility, and annoyance, but only for males with high trait levels of aggression (Cleare and Bond, 1995). Lastly, Marsh et al. (2002) found, using a similar design (2.3 g of TRP added to 100 g of amino-acids) but including only females, that TRP administration significantly reduced aggressive responses in an aggression-provoking task (Cherek et al., 1996) when compared to a control condition (i.e., a low monoamine diet). Overall, these findings suggest TRP may modulate aggressive behavior, although effects may strongly depend on gender and personality characteristics (e.g. trait levels of aggression). The lack of consideration of these factors may explain why other studies failed to observe any effect of TRP on aggression (Smith et al., 1986; Bjork et al., 1999).

TRP supplementation also seems to be beneficial for male children with a history of physical aggression and behavior regulation difficulties such as ADHD. Using a double-blind procedure, Nantel-Vivier et al. (2011) compared two groups of boys with a history of elevated physical aggression with regard to provocative, impulsive, and affiliative behavior, perspective taking, and emotion recognition. One group received an acute 0.5 g dose of TRP, while the other group received a neutral placebo. All children then played a game against the computer, although they thought they were playing against another person. In this game, participants have to press the space bar as fast as they can upon seeing a cue. When being the fastest of the two, points can be earned and the participant is allowed to choose how many points they want to deduct from the other person and transfer to a neutral 'bank'. However, when the participant themselves are the slowest one, either no, a few, or a lot of their own points can be deducted by the computer, resulting in no, low, or high provocation conditions, respectively. Results showed that, compared to the placebo group, children in the TRP condition showed optimal adjustment of responding corresponding to the degree of provocation. That is, compared to baseline, boys in the TRP condition decided faster and took away more points from the computer when the boys themselves were highly provoked, making the game more fair. No differences were found in the no or low provocation conditions. In addition, the TRP group showed less impulsive behavior, a trend towards greater perspective taking, and was better able to distinguish between facial expressions of fear and happiness (Nantel-Vivier et al., 2011). Similarly, several decades ago Nemzer et al. (1986) showed parents reported an improvement in behavior (i.e., lower impulsivity and higher concentration) of their children with ADHD after one week of 100 mg/kg TRP per day, as assessed by the Conners Parent's Questionnaire (Conners, 1970) and the Quay-Peterson scale (Quay and Peterson, 1967). Since 5-HT may play a role in ADHD (Oades, 2008) and ADHD is associated with antisocial behavior (Richards et al., 2015), TRP supplementation might be of interest for attention deficit disorder with hyperactivity (ADHD).

In sum, TRP may be used to alleviate psychiatric and neurological disorders and antisocial behaviors associated with suboptimal or dysfunctional serotonergic levels. It may help patients and individuals at risk for decreased social functioning to gain more control over social interactions (Moskowitz et al., 2011) and to show less impulsive, antisocial behavior. Indeed, the reported findings are in line with the idea of a key role of 5-HT in inhibiting responses to stimuli such as provocation (Soubrie, 1986; Spoont, 1992; Young, 2013), possibly by inducing a bias towards positive instead of negative stimuli. However, it is worth noting that effects of TRP on measures related to social behavior in clinical populations are not yet straight-forward and predictable, as evidenced by counterintuitive results in individuals at risk for depression. It would be valuable for future studies to investigate whether results are more consistent when considering social context, the behavior of interaction partners, and the myriad of modulating factors discussed later in the section "Factors modulating TRP effectivity".

### 2.2. Healthy humans: promoting social behavior

In this section we describe studies suggesting that TRP can have promising implications for healthy individuals in promoting social behavior. A placebo-controlled study by aan het Rot et al. (2006) reported the intake of TRP (1 g, 3 times a day, for 15 days) lessened quarrelsome and enhanced agreeable behavior and perceptions of agreeableness. In addition, a placebo-controlled study by Moskowitz et al. (2001) investigated the effect of 12 days of TRP supplementation (1 g). TRP augmented dominant behavior independent of treatment order, an effect also found in monkeys (for a review see Watanabe and Yamamoto, 2015). Further, TRP reduced quarrelsome behavior but only when given after the placebo treatment. The authors argued this might be explained by the possibility that effects of TRP on cognitions and social behaviors prolonged even after TRP intake had stopped and placebo intake was started. Indeed, the authors suggested that it is possible

that TRP changed reciprocal interactions of participants and their acquaintances. This highlights the need for baseline measures of behavior, as we will propose later, to detect any changes following TRP intake.

TRP has also been shown to modulate behavior in economic decision-making tasks such as the ultimatum game (Güth et al., 1982) and the trust game (Camerer and Weigelt, 1988; Berg et al., 1995). These games exemplify important concepts related to social behavior, including empathy, fairness, and altruism (Ebstein et al., 2010). For instance, the ultimatum game taps into the trade-off between decisions motivated by fairness versus selfishness. In this game, participants are usually asked to make a proposal with regard to a distribution of money among the participant and another player, and/or to accept or reject a proposal by another (fake) participant. If the proposal is not accepted, both players receive nothing. A study by Cerit et al. (2015), in which participants received 2.8 g of TRP or placebo for six days, suggested no significant effect of TRP on behavior in the ultimatum game. However, an additional analysis in which seven participants who accepted all offers post-intervention were excluded showed an increase in rejections of very unfair offers in the TRP group compared the placebo group. As pointed out by the authors, this outcome seems to challenge idea that TRP can promote prosocial behavior, although it may be explained by the fact that on the testing day participants did not consume TRP. Specifically, according to the authors, this may have caused a relative depletion as compared to previous days, thereby inducing an outcome that one would expect as a consequence of TRP depletion (Crockett et al., 2008). However, a fact questioning this possibility is that, within the same study, TRP supplementation was also found to reduce the physiological response to stress (i.e., cortisol level; for consistent results, see also Cerit et al., 2013). Indeed, cortisol responses are strongly related to the automatic processing of emotional information (Ellenbogen et al., 2010), with lower cortisol responses indicating less reactivity to stressors. Therefore, the lower cortisol response to stressors following TRP, as found in the study by Cerit et al. (2013, 2015) is might indicate TRP supplementation induced a positive bias in information processing, which does not fit with the relative depletion account advocated by the authors. An alternative interpretation of the finding that TRP increased instead of reduced rejection rates is related to the idea that reciprocity is important for cooperation, which consists of a combination of altruistic rewarding and altruistic punishment (i.e., imposing sanctions on others who violate norms; Fehr and Fischbacher, 2003). As such, if one considers the rejection of unfair offers to reflect altruistic behavior, i.e. altruistic punishment, then an increase of rejections after TRP can in fact represent a form of prosocial behavior.

Finally, research has found TRP can promote interpersonal trust as measured in a trust game—a task that quantifies the extent to which one participant (the trustor) trusts another participant (the trustee), as indicated by money transferred from trustor to trustee (Camerer and Weigelt, 1988). In line with the idea that TRP supplementation might promote agreeable, prosocial behavior, after the ingestion of 0.8 g TRP, participants transferred significantly more euros to the trustee than after intake of the placebo, an indication of increased interpersonal trust (Colzato et al., 2013). Consistent with these findings, acute TRP supplementation (0.8 g) has also been found to promote charitable donating by almost doubling the amount of money participants donated to charity, as compared to the placebo condition (Steenbergen et al., 2014).

All in all these results suggest that TRP supplementation, resulting in enhanced 5-HT functioning, has promising potential to promote positive social, i.e. agreeable, prosocial behavior.

## 3. Factors modulating TRP effectivity

As mentioned in the Introduction, TRP effects on 5-HT synthesis and functioning seem to depend on a variety of factors, such as the competition between LNAAs (see “Mechanism of action” section), neuronal activity, enzymatic activity, genetic variability, gender, age, and the amount of TRP contained in one’s diet (Young, 2013). These factors potentially explain part of the variability in TRP effectivity, both within and between individuals.

It has been shown that, at least in animals, the intake of TRP significantly decreases the firing rate of serotonergic neurons (Trulson and Jacobs, 1976). Interestingly, this is also the case for the administration of selective serotonin reuptake inhibitors, which are supposed to increase 5-HT availability in the synapse (Fischer et al., 2015). Altering serotonergic levels via TRP supplementation is most likely to influence the rate of 5-HT release when neurons are firing at a high rate (Trulson and Jacobs, 1976). This leads to the possibility that effects of TRP administration might be most effective in circumstances under which the firing rate of 5-HT neurons is increased, for instance when showing a high level of behavioral arousal (Young et al., 1988; Young, 2013), which, at least in animals, has been found to determine the amount of release of 5-HT (Rueter et al., 1997). However, in the aforementioned study by Pihl et al. (1995), in which arousal levels were supposedly increased by delivering shocks to the participants before being confronted with an aggression-provoking task, effects of TRP were only observed in the low arousal condition (i.e., when the intensity of the shocks was below the pain threshold) but not in the high arousal condition (i.e., when the intensity of the shocks was above the pain threshold). This suggests that the supposed relationship between arousal levels and TRP efficacy may apply only to situations in which arousal levels are moderately high.

As the TPH enzyme is essential to converting TRP into 5-HT, it is important to consider the conversion of TRP takes place in two locations via two different types of enzyme: the gut (TPH1) and the brain (TPH2) (Walther et al., 2003). Since 5-HT cannot pass the BBB whereas TRP can, all available 5-HT in the brain depends on the conversion of TRP to 5-HT by TPH2 after TRP has passed the BBB. Hence, if the TPH1 enzyme in the gut is very active, more TRP is converted there and less will be available to pass through the BBB and be converted into 5-HT in the brain. Thus TRP might have less impact on social behavior in individuals with highly active TPH1 enzyme.

Another source of variability in the effectiveness of TRP supplementation may be vitamin B and D availability. Indeed, activation of the TPH2 enzyme, involved in the first step of the conversion of TRP into 5-HT in the brain (Walther et al., 2003; Gutknecht et al., 2009), depends on vitamin D hormone availability (Haussler et al., 2011; Hsieh et al., 2013; Patrick and Ames, 2014). Also, the decarboxylase enzyme involved in the last step of the conversion of TRP in 5-HT needs vitamin B6 (pyridoxine) as a cofactor in order to convert 5-HTP into 5-HT. Accordingly, even though vitamin B6 is not a precursor of 5-HT, it can be considered a rate-limiting factor in the final step of 5-HT synthesis (Calderón-Guzmán et al., 2004; Deac et al., 2015). For these reasons, it is often advised to take vitamin B and D supplements along with TRP. It is possible TRP might have reduced effectivity in individuals with deficient vitamin B and D levels.

Furthermore, variations in genes associated with serotonergic functioning might contribute to inter-individual variability in response to TRP. Two examples of relevant genes are the TPH gene and the serotonin transporter gene (5-HTTLPR). In the TPH gene, the A-C polymorphism seems to play an important, functional role. Although the exact role of this gene in the activity of TPH is unclear, A-carriers (A2051C) have lower levels of 5-HIAA, the main metabolite of 5-HT, as compared to C-carriers (Chen

et al., 2010), suggesting reduced 5-HT transmission. In addition, A-carriers (A218C and A779C) show higher levels of aggression and explicit anger (Manuck et al., 1999; Reuter and Hennig, 2005). These findings suggest two contrasting hypotheses regarding the potential effect of this polymorphism on TRP effectivity. On the one hand, A-carriers demonstrate elevated levels of aggression and explicit anger, suggesting much room for improvement following TRP supplementation. Alternatively, their reduced 5-HT activity might actually lead to less impact of TRP based on the hypothesis that TRP is especially effective when the firing rate of serotonergic neurons is high. Currently it is not yet clear if and in which direction this polymorphism predicts response to TRP supplementation and more research would be valuable to answer this question.

The second functionally relevant polymorphism is in the 5-HTTLPR gene, which can have either long (l) or short (s) alleles. In homozygotic carriers of the "l" allele, expression of the serotonin transporter (5-HTT) is higher and the reuptake of 5-HT is almost double as compared to heterozygous or homozygous carriers of the "s" allele (Heils et al., 1996). This increased reuptake of 5-HT suggests l-carriers have less 5-HT activity than s-carriers, but, counterintuitively, s-carriers seem to be the ones who have lower 5-HT function (Bethea et al., 2004). Correspondingly, they demonstrate increased risk for depression (Caspi et al., 2003) and higher levels of trait anxiety (Lesch et al., 1996). It has been proposed the counterintuitive effect of transport availability on serotonergic activity may be due to the polymorphism's effect on early brain development (Bethea et al., 2004), leading to adaptions persisting into adulthood. Since s-carriers have reduced 5-HT function, it is possible they are more reactive to 5-HT manipulations (Cerit et al., 2013) and benefit more from TRP supplementation than l-carriers. However, as is the case with the TPH polymorphism, it is also possible reduced 5-HT activity might actually lead to less effect of TRP, as TRP might be most effective in neurons with high firing rates. In contrast, one study showed TRP reduced the physiological response to social stress in s-carriers, but not l-carriers (Cerit et al., 2013). Thus, it seems that s-carriers may benefit more from TRP supplementation than l-carriers. Furthermore, it is important to note there is an A-G polymorphism in the "l" allele of the 5-HTTLPR gene, leading to the distinction between an "$l_A$" and "$l_G$" variant, with the "$l_G$" variant being functionally similar to the "s" allele (Hu et al., 2006). This raises the possibility that both the "s" and "$l_G$" allele may be associated with stronger responses to TRP supplementation. Hence, disregarding the A-G polymorphism in the "l" allele might lead to an underestimation of the 5-HTTLPR gene's influence on TRP supplementation. For this reason we strongly recommend future studies to consider both these polymorphisms, to explain variability in TRP response within samples and across studies.

Another potential determinant of TRP effects is inter-subject and inter-sample variability in several factors. For example, variation in body mass index (BMI) might lead to different substance concentration levels when the same dose is given to all participants. Interestingly, only one of the above discussed studies included individualized dosages (Nemzer et al., 1986). It would be interesting to investigate whether individual differences in TRP effectivity might perhaps be explained by an individual's BMI. This would promote the use of individualized dosages (e.g. a dosage of X mg/kg of bodyweight instead of the same dosage for everyone), thereby increasing the chance to demonstrate consistent and replicable findings with TRP. Moreover, gender might modulate the efficacy of TRP supplementation, since 5-HT synthesis seems to be lower in females than in males (Nishizawa et al., 1997; Sakai et al., 2006). Consistent with this finding, TRP depletion lowered mood in women but not in men (Ellenbogen et al., 1996). Furthermore, age can significantly influence both serotonergic functioning and (pro) social behavior. For instance, ageing has been related to decreases in 5-HT availability, receptors, transporters, and enzymes (Fidalgo et al., 2013). In addition, at least in animals, aging and age-related diseases are associated with unbalanced TRP metabolism (Van der Goot and Nollen, 2013). However, empathy and prosocial behavior have been found to improve with increasing age (Sze et al., 2012), although as pointed out by the authors themselves, a cross-sectional design cannot exclude the possibility that reported age differences in empathy and prosocial behavior may in fact be explained by historical factors or contemporary social roles instead of age per se. For instance, in this study, study members of the older cohort grew up just after the second world war, and their experiences of being in need and experiencing distress in those times might have contributed to enhanced empathy and more prosocial behavior towards others in need. Additionally, old age might be associated with reduced self-sufficiency and, as a consequence, increased dependency on more prosocial behavior towards others. In sum, more longitudinal research that also takes into account contemporary social roles is needed to disentangle and understand the relation between TRP, 5-HT, ageing, and social behavior.

Lastly we would like to stress the importance of baseline levels of social behaviors or related measures. This suggestion is based on the finding of Crockett et al. (2010), who showed citalopram only affected moral judgments in those who reported higher baseline empathy levels. Given that one mechanism by which TRP could act is through the biasing of information processing towards positive stimuli, this suggests that in individuals with low 5-HT, the initial bias towards negative stimuli might be greatest and hence they could benefit most from an increase in 5-HT. However, evidence for a relation between TRP efficacy and initial 5-HT state is still controversial (Silber and Schmitt, 2010). Related to the previous point, extensive research is needed to investigate the possible long-term effects of TRP. This issue is particularly important when placebo-controlled within-subjects designs are implemented, as it may help to set the appropriate distance between two or more critical sessions (e.g., placebo and TRP; for evidence suggesting the importance of this issue, see e.g., the results reported by Moskowitz et al., 2001).

## 4. Conclusion

As the biochemical precursor of 5-HT, TRP has the potential to enhance serotonergic function in the brain. There is promising utility of TRP supplementation for patients or individuals suffering from disorders or behaviors related to dysfunctions in the 5-HT system, as TRP might help improve control over negative social behavior such as aggression, although studies on this issue are still limited. There is also promising potential of TRP for promoting positive social behavior such as agreeableness, sharing, helping, donating in healthy humans. This suggests TRP supplementation may be a useful tool to enhance social functioning in inexpensive and efficient ways.

TRP, through stimulating 5-HT synthesis, possibly acts by inducing a positive bias in information processing, leading to more attentiveness to positive stimuli and, as a consequence, less negative (e.g. aggressive), social behavior. This suggests the effect of TRP on social behaviors may be strongest for individuals with low baseline 5-HT functioning, as their initial bias towards negative stimuli might be greatest. However, evidence for this relation between TRP efficacy and initial 5-HT state is still controversial (Silber and Schmitt, 2010).

It is important to acknowledge that, aside from inducing a bias in information processing, the modulating effect of TRP on social behavior might also be mediated by other pathways. For instance, TRP administration and increases in brain TRP are also associated with better quality of sleep and better mood (for a review see Silber and Schmitt, 2010), which might impact behavior in several ways. The relationship between TRP and quality of sleep is not surpris-

ing if one considers that 5-HT is also the precursor of melatonin, which plays an important role in regulating the sleep-wake cycle (Richardson, 2005). Furthermore, TRP is reckoned to have a mild sedative effect, possibly due to the increase in melatonin production associated with the increase in 5-HT levels (Ruddick et al., 2006; Bravo et al., 2012). Such a relation may explain, for example, the positive effects that TRP can have on impulsive behavior (Silber and Schmitt, 2010).

The relation between TRP and mood may represent an alternative pathway through which TRP can affect social behavior. As pointed out by Young (2013), given that increases in 5-HT may have positive effects on mood, and as better mood is typically associated with more positive social interactions, the effects of TRP in promoting social behavior may just reflect the consequence of better mood following TRP intake, though the opposite may be true as well.

Interestingly, improved sleep and mood are related to reduced stress and better coping abilities (e.g. Markus et al., 2000). When experiencing stress, people tend to behave and process information in ways that are less resource demanding (Starcke and Brand, 2012). As taking into account the mental states of others can be considered resource demanding (e.g., Epley et al., 2004), a stressed individual may tend towards behaviors and processes that are more egocentric or self-centered (i.e., to behave less prosocially; but see von Dawans et al., 2012)—a possibility that, however, may apply only to men, as females seem to be able to express accurate social responses during stress; Tomova et al., 2014). Therefore, one may argue that, at least in men, TRP may improve social behavior by reducing stress. However, the lack of a straightforward relation between TRP, stress and social behavior makes this possibility highly speculative.

Taken together, the aforementioned observations cannot allow one to rule out that at least some of the effects of TRP administration on social behavior might in fact be a result of enhanced sleep and mood, and/or reduced stress. This warrants further investigations in order to understand the potential role of these factors in mediating TRP effects on social behavior.

Another important consideration pertains to the fact that TRP can be metabolized not only through the 5-HT pathway but also through the kynurenine (KYN) pathway. In fact, outside the central nervous system, only one percent of dietary TRP is converted into 5-HT. That is, the majority of TRP is catabolized along the KYN pathway (Russo et al., 2003). In the first step of this metabolic way, TRP is transformed into KYN. Next, KYN is converted to a series of metabolites, such as 3-hydroxykynurenine and quinolinic acid (for a detailed explanation of this oxidative pathway, see Russo et al., 2003). Interestingly, KYN can pass the BBB and lead to the production of neuroactive metabolites that modulate glutamatergic and cholinergic signaling (Capuron and Miller, 2011), suggesting TRP effects are not mediated solely by 5-HT. This might be particularly true for females suffering from irritable bowel syndrome, as they show an increase of TRP catabolism along the KYN pathway, which contributes to the abnormal 5-HT functioning in this syndrome (Fitzgerald et al., 2008). Indeed, TRP depletion has shown to reduce KYN levels in females with irritable bowel syndrome, which impaired visuospatial memory performance (Kennedy et al., 2015). Hence, taking into account individual differences in TRP metabolism (e.g. the amount of TRP metabolized via the KYN pathway vs. the 5-HT pathway) may provide important insights into the effectivity of TRP in modulating social behavior.

We would like to point out that in laboratory studies such as the ones discussed in this review, social behavior is typically measured by attitudes, behavioral indicators of helping or self-reported intent to help, aggressiveness, etc. However, more direct behavioral measures such as charitable donating (Steenbergen et al., 2014) and aggressive incidents (Morand et al., 1983) are sometimes used as well. Aside from the possibility that attitudes assess socially desirable responses and not behavior per se, the variability in measures used to assess social behavior makes the reviewed studies hard to compare. We would therefore like to call for more direct measures of social behavior to be used in future studies on TRP supplementation, as this may help gaining a better understanding on how TRP can affect social behavior in real-life situations, outside the lab. In addition, other measures of prosocial behavior that have not yet been investigated in relation to TRP, such as how much time people are willing to spend with others (Farrelly et al., 2015), could be considered as well.

Although more research is needed to disentangle and understand the relation between individual differences, TRP effectivity, 5-HT functioning, and social contexts and interactions, we conclude TRP can be an effective method of modulating social behavior.

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## Conflict of interest

The authors declare that there are no conflicts of interest.

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