

# Exploring the Effects of Tomato Extract Supplementation on Cognitive Function during Exercise and at Rest

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## Abstract

It has been reported that tomato (*Solanum lycopersicum*) fruit extracts may have beneficial effects on cognition. To assess if those effects are reproducible, cognitive function was assessed using a double-blind, randomised control trial design; 17 healthy test participants were given encapsulated tomato fruit (n=8) extract (290 mg) or a placebo control (n=9). Cognition was assessed at rest and, as exercise is known to negatively impact on cognitive function, equivalent tests were also undertaken after controlled physical exertion using the Bath University Rugby Shuttle Test (45 minutes and 90 minutes exercise).

After normalisation of raw data to remove performance related error, the tomato fruit extract improved ( $P < 0.05$ ) normalised detection scores and detection times after 90 minutes exercise. These positive effects were specific to psychomotor function, relating to both ability and speed of response; compared to placebo controls, the supplemented group recorded scores 6.5% ( $P = 0.02$ ) and speeds ~17% ( $P = 0.03$ ) better when compared to the placebo group. A repeated measures linear mixed model (LMM) was undertaken and again significance reported ( $P < 0.05$ ) for overall effects of treatment (detection speeds and scores) and additionally for the identification speed. A suggestion ( $P < 0.1$ ) of treatment effects was observed for identification scores. LMM analysis therefore also identifies positive benefits for reaction times and visual attention after supplementation. No effect on one-card-learning (visual learning) scores or speeds was detected; also there is no evidence of any learning effect on the data. Collectively this data shows certain tomato fruit extracts have a trait specific beneficial effect on cognition.

**Keywords:** Cognition; Tomato; Exercise

## Introduction

Cognition consists of mental processes such as memory, learning and psychomotor function. It represents a complex polygenic phenotype, traits which intersect many different gene pathways and biological processes. A number of approaches have been trialled to improve or maintain cognitive function; including supplements that alter or stimulate synaptic function or brain training programs designed to improve performance for specific tasks [1]. New compelling research shows that dietary or nutritional considerations may be important in maintaining or improving cognitive function in both young and older age groups; in health survey analysis consumption of fruit and vegetables associated with better cognitive performance and could also help protect against cognitive decline [2]. Supplements such as leaf, fruit or herb extracts have also been tested for effects on cognition with some success. Some studies suggest that *Ginkgo biloba* supplements may provide added cognitive benefits to individuals presenting with dementia, although effects of supplement are not observed in all patients tested [3]. Cognitive testing of rosemary (*Rosmarinus officinalis*) identified a range of effects including a statistically significant ( $P = 0.01$ ) beneficial effect on speed of memory recall when compared to placebo [4]. Conversely higher doses had a statistically significant negative impact on this trait ( $P = 0.01$ ). Supplements containing tomato have also been trialled. Forty healthy subjects were supplemented with a beverage based on a mixture of fruit (150g blueberries, 50g blackcurrant, 50g elderberry, 50g lingonberries, 50g strawberry, and 100g tomato). Subjects performed better in working memory tests after consuming the fruit beverage compared to control ( $P < 0.05$ ) [5]. Proof of concept research testing tomato extract also identified cognitive benefits within rodent trials designed to replicate cognitive decline observed in aging [6]. Amelioration of cognitive impairment was also observed after supplementation with tomatoes *in-vivo* when cognition deficits were induced in rodents with D-galactose [7]. D-galactose is used to model cognitive impairment via its effects as an inducer of oxidative stress and senescing effects in neuronal cells [8].

Exercise is also known to affect cognition. One such example is exercise induced fatigue which may be detrimental to both cognitive function and motor skills [9]. This process may in-part be due to elevated levels of oxidative stress, which negatively affect cognitive abilities via synaptic damage and interrupted cell-cell communication [10,11]. Inflammation may also negatively link to cognitive ability and specific components of the immune system such as Interleukin 6 (IL-6) were negatively associated with performance on tests such as Mini Mental State Exam [12]. Interestingly IL-6 is also upregulated and secreted into the circulatory system by exercise [13].

Beneficial effects of tomato consumption have been shown when tomato is a component ingredient, however little is known about the effects of tomato when dosed as a single supplement. The aim of this study was therefore to assess effects on cognitive performance of supplementation with a tomato based extract (TE), either before or during exercise.

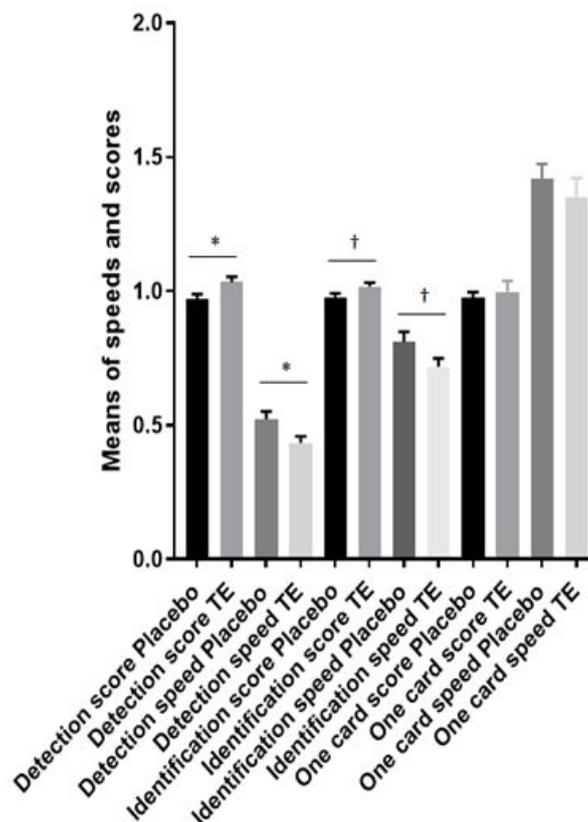
## Materials and Methods

### Study Design

Ethical approval was granted by the St. Mary's University ethics committee. The experimental design incorporated a double-blinded randomised control and was undertaken using published cognitive tests. After receiving a full explanation of the test requirements and risks, 17 healthy recreational team sports players (age;  $28 \pm 4$  years, weight;  $84.9 \pm 9.8$  kg, height;  $179.7 \pm 8.6$  cm) provided written informed consent and participated in the study. All participants completed a medical screening questionnaire before testing began. In the days preceding the trial, participants were instructed to maintain a normal diet, and also asked to refrain from caffeine and alcohol consumption in the 24 hrs prior to the tests.

### Treatment Regimen

In the double-blinded, randomised control trial, participants were randomly assigned to either a placebo (n=9) or a tomato extract supplementation group (n=8) (TE). Tomato fruit were harvested, freeze dried and milled to a fine powder. Testing identified that 100mg of powdered extract of TE contained 80mg carbohydrate, 5 mg water, 4 mg protein and fat content was below 5 mg. Participants consumed one capsule containing either 290 mg dosage of the powdered supplement plus 10mg magnesium stearate and 110mg cellulose or an equivalent placebo control. Capsules were taken with water, 60 min prior to the commencement of the test (at rest); identical packaging and capsules were used for both placebo and TE. The dosage was in line with European Food Safety Authority daily dosage recommendations (efsa.europa.eu). No adverse effects or side effects were reported after consumption of the TE containing capsules, either after dosing with no exertion or consumption of TE combined with exercise.



**Figure 1:** Normalised data for placebo and TE group across after 90 minutes exercise. In the TE group, statistically significant improvements were observed (ANOVA) in both co-normalised detection score and detection time at this time point (\* denotes  $P < 0.05$ ). Normalised identification scores and speeds trended toward significance († denotes  $P < 0.1$ ), whereas no effect was observed for normalised one card learning scores and speeds.

Participants completed an adapted version of the Bath University Rugby Shuttle Test (BURST) (see supplementary Figure 1). The BURST is a rugby union-specific match-play simulation protocol, designed to replicate the physical demands of elite rugby union forwards [14]. The requirements of the exercise protocol have been detailed elsewhere [14].

In brief, the adapted protocol comprised 8 x 300s blocks followed by a 20min “half time” period (rest) followed by a further 8 x 300s blocks (total time 80 min)(see supplementary Figure 1). Each 300s block consists of participants repeatedly performing shuttles of walking (20m), cruising (20m), jogging (10m) and sprinting (10m) which consists of a 1 x maximum sprint (20m) within the last 30 sec of each block.

A 15 minute computerised cognitive test battery (CogState Ltd., Melbourne, Australia) was administered to all participants prior to, at half-time and following the adapted simulated rugby match protocol. CogState is a validated tool for measuring cognitive impairment induced by mental fatigue. Cogstate tests are reported to be culture-neutral, are not limited by a subject's level of education and are designed for repeated administration with minimal practice or learning effects (see [www.cogstate.com/clinical-trials/](http://www.cogstate.com/clinical-trials/) for further information). The cognitive test battery included the following specific tasks: The detection task measured reaction time, psychomotor function and information progression. The identification task measured reaction time and visual attention. One-back working memory measured visual learning and memory. The delayed recall task measured continuous retention and recall. Attention task measured the ability to maintain focused attention. Performance was measured in terms of time or accuracy. Each task used playing cards as stimuli which are designed to have almost infinite equivalent alternative forms [15]. A familiarisation or practice was included prior to each task. Once individuals are familiar with the test, it shows no practice effects [16].

### Metabolite Analysis

Carotenoids and tocopherols were extracted from freeze-dried fruit (n=3) using chloroform and methanol (2:1) following the protocol described in [17]. Carotenoids were separated and identified by Ultra High Performance Liquid Chromatography with photo diode array detection (UPLC-PDA). The separation, detection and quantification of carotenoids, tocopherols and chlorophylls have been described previously [18]. Extraction and analysis of intermediary metabolites followed protocols described in [19,20].

### Statistical Analysis

The data analysis for this paper was generated using Genstat software (Release 19.1) VSN International Ltd. A Kolmogorov-Smirnov test was undertaken to determine normality. An analysis of covariance (ANOVA) was used to compare the effects of both TE and placebo on four key cognitive performance variables (detection, identification, one card learning & one back time) at each of the three time points (at rest, and after 45 minutes and 90 minutes exercise). Confidence intervals of 95% are also described in the text for significant values and error bars represent standard error of the mean. A repeated measures linear mixed model (LMM) was undertaken on cumulative speeds and scores across three time points.

## Results

### Raw Data Testing at Rest and after Exercise

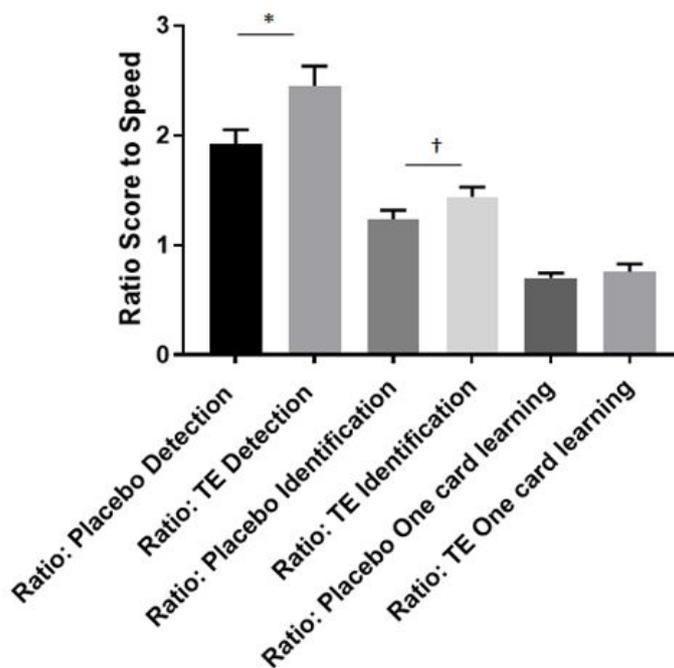
Treatment with an encapsulated TE was first tested for any effect in enhancing cognitive function both at rest and after exercise. Cognitive performance variables tested included detection, identification, one-card-learning and one back time. In these tests an increased score is associated with a positive response, whereas increased time is associated with a negative response. No significant effects of treatment were observed across a number of different raw tests scores and speeds (see Supplementary Table 1).

		At Rest				After 45 minutes exercise				After 90 minutes exercise			
		Detection				Detection				Detection			
		Score		Speed		Score		Speed		Score		Speed	
		Mean	± S.E.M	Mean	± S.E.M	Mean	± S.E.M	Mean	± S.E.M	Mean	± S.E.M	Mean	± S.E.M
Placebo	Normalised	0.95	0.04	0.60	0.10	0.99	0.00	0.49	0.01	0.97	0.02	0.52	0.03
Treated	Normalised	1.02	0.02	0.43	0.03	1.03	0.01	0.39	0.05	1.03	0.02	0.43	0.02
		Identification				Identification				Identification			
		Score		Speed		Score		Speed		Score		Speed	
		Mean	± S.E.M	Mean	± S.E.M	Mean	± S.E.M	Mean	± S.E.M	Mean	± S.E.M	Mean	± S.E.M
		Placebo	Normalised	1.01	0.01	0.70	0.03	1.00	0.01	0.76	0.01	0.98	0.02
Treated	Normalised	1.04	0.02	0.67	0.04	1.04	0.03	0.68	0.05	1.02	0.01	0.72	0.03
		One-card learning				One-card learning				One-card learning			
		Score		Speed		Score		Speed		Score		Speed	
		Mean	± S.E.M	Mean	± S.E.M	Mean	± S.E.M	Mean	± S.E.M	Mean	± S.E.M	Mean	± S.E.M
		Placebo	Normalised	0.98	0.02	1.40	0.08	0.96	0.03	1.31	0.06	0.98	0.02
Treated	Normalised	0.95	0.04	1.43	0.05	1.04	0.04	1.56	0.06	1.00	0.04	1.35	0.07

Table 1: Co-normalised data to one back test scores and speeds for each time point, either at rest or after exercise

### Co-Normalised Scores at Rest and after Exercise

Although no differences in raw detection score and times in detection were recorded, it was hypothesised that performance related error may be a limiter for the identification of meaningful change in performance. Research has identified that the action of undertaking a test or the complexity of the technological platform used to measure ability can introduce non-physical performance related error (Table 2). Therefore the data was co-normalised for each individual to an appropriate internal test measure i.e. a test conducted using the same test platform that shows [21,22], no group wide aggregate difference; either between groups or changes in pre to post exercise. The test chosen was one back test (Figure 2).



**Figure 2:** Relationship between score achieved and response time plotted as a percentage of placebo. The ratio score to speed is significantly higher (ANOVA) at 90 minutes for detection (P=0.03) i.e. a higher score was achieved in a faster time. A similar phenomenon was observed for the identification test, which trended towards significance (P=0.1)

	Detection				Identification				One card learning			
	Score		Speed		Score		Speed		Score		Speed	
	Mean		Mean		Mean		Mean		Mean		Mean	
Treat Standard error of differences F pr	Active	Placebo	Active	Placebo	Active	Placebo	Active	Placebo	Active	Placebo	Active	Placebo
	1.026	0.969	0.439	0.539	1.031	0.994	0.690	0.772	0.989	0.971	1.369	1.376
	0.027		0.046		0.018		0.037		0.041		0.071	
	0.047		0.047		0.059		0.041		0.724		0.941	

**Table 2:** A repeated measures linear mixed model test identifies significance in detection scores and speeds, plus identification speed. A trend towards effect was reported for identification scores

At rest detection scores and speeds were not significantly different (P=0.25; P=0.17) and no difference was detected in either identification scores or speeds (P=0.21; P=0.14) or one card learning scores or speeds (P=0.61; P=0.82). After 45 minutes exercise detection scores and speeds were also not significantly different (P=0.25; P=0.31). However a trend (P=0.1) was observed for identification scores (TE 1.03 ± 0.01 vs Placebo 1.0 ± 0.01) and speeds (P=0.06, TE 0.68 ± 0.03 vs Placebo 0.76 ± 0.02). One card learning scores or speeds showed no variation at this time point (P=0.11; P=0.74).

Interestingly however, after 90 minutes exercise a positive effect of TE supplementation was identified specific to psychomotor function; relating to both ability and speed of response; compared to placebo controls, the supplemented group recorded scores 6.5% (P=0.02) and speeds ~17% (P=0.03) better than the placebo group (score: TE 1.03 ± 0.01 vs placebo 0.97 ± 0.01 (P= 0.02; [Lower 95%CL 0.0075, Upper 95% CL 0.1184]; speed: TE 0.43 ± 0.02 vs placebo 0.52± 0.03 (P=0.03; [Lower 95% CL -0.1690, Upper 95% CL -0.0049]. Trends were also observed in improvements for identification speeds and scores (score: TE 1.02 ± 0.02 vs placebo 0.98 ± 0.01 (P=0.08); speed: TE 0.72 ± 0.03 vs placebo 0.81±0.03 (P=0.08).

For detection and identification testing, a greater score was matched by a lower speed relative to placebo; therefore it was of interest to calculate the ratio of score to speed i.e. the length of time taken to record a score (Figure 2). The ratio of detection speed to scores showed a significant change (P<0.05) after 90 minutes exercise and identification (P=0.1) score to speed ratios trended towards effects relative to the placebo control after 90 minutes exercise.

A repeated measures linear mixed model (LMM) was then undertaken on normalised data and again significance reported ( $P < 0.05$ ) for overall effects of TE for detection speeds and scores and additionally for the identification speed. Analysis identified a suggestion ( $P < 0.1$ ) of treatment effects for identification scores. LMM analysis therefore also identifies positive benefits for reaction time and visual attention after supplementation. No effect on one card learning (visual learning) scores or speeds was detected; also there is no evidence of any learning effect on the data. In addition there was a suggestion of effect ( $p < 0.1$ ) of a treatment and time effect on the identification score. No evidence of any learning effect was identified within the data.

## Metabolite Analysis

Metabolomics testing identified detectable levels of key metabolites associated with tomato fruit; Lutein ( $51 \pm 0.3 \mu\text{g per g}$ ), Lycopene ( $1459 \pm 23.5 \mu\text{g per g}$ ),  $\alpha$ -Tocopherol ( $79 \pm 2.8 \mu\text{g per g}$ ). Low levels of sugars such as pentose ( $0.0009 \pm 0.0002 \mu\text{g per mg}$ ), Fructose ( $2.3 \pm 0.06 \mu\text{g per mg}$ ) and Glucose ( $1.6 \pm 0.07 \mu\text{g per mg}$ ) were also detected.

## Discussion

Cognitive function can be of great importance during exercise and lapses in concentration, decision making and skill performance are common [23,24]. Whilst this is often visually apparent through decreased physical performance and a decrease in work rate, it is also evidenced through deterioration in physical coordination, skill, and a reduced ability to perform movements that require skill and concentration. Although reasons for this are often linked to a decrease in the availability of energy, carbohydrate availability and fluid [25], cognitive function may also contribute to decreased ability in a range of different tasks.

Improvements were identified in both relative scores and times for a number of co-normalised data i.e. statistically significant changes relative to an independent cognitive trait, including changes in the ratio between scores and time. Although these gains were limited to tests conducted after exercise and little effect was observed at rest. Tomato extracts have previously been shown to impact on various aspects of cognition in rodent models and in limited human trials [6], therefore the data is consistent with previously recorded studies. Improvements at test points conducted after exercise for detection and identification measures suggests that these effects may link to exercise.

Co-normalisation can act to reduce personalised effects due to the test platform itself, present when using this type of technologically based cognitive test setup together with relatively small cohort sizes. The data here shows that relative to one trait (working memory); significant changes in other cognitive traits were observed after exercise. As no intragroup or intergroup variability was recorded for one card learning, and as working memory has been shown not to be negatively impacted by exercise [26], the interpretation is that this test therefore provides an appropriate means of assessing each individual's ability to appropriately use the test facilities. Intriguingly, the process of normalising to working memory suggests significant differences between TE and placebo groups identified within this data link to psychomotor traits, reaction times and visual attention (detection and identification tests) but not visual learning skills i.e. one-card-learning after 90 minutes exercise.

The data presented in this study supports prior research conducted into the cognitive benefits associated with berry and fruit supplementation [5]. Albeit this research identifies beneficial effects associated with different cognitive traits. There are a number of possible explanations for the results observed in this study. It is plausible that the extract exerts an anti-oxidant effect and this is sufficient to boost cognitive function or mitigate impairment when participants are subject to exercise. Compounds present in tomato such as lycopene and  $\beta$ -carotene have anti-oxidant properties; however links between anti-oxidants and cognitive function are conflicting with some reports showing little benefit of supplementation [27]. Antioxidant treatments also fail to show additive or antagonistic effects in models designed to show changes in cognition linked exercise [28]. Although it is plausible that component antioxidants contribute to those beneficial effects described for improvements in scores and speeds, it is unlikely that antioxidants alone are responsible for the effects described in this study.

Interestingly some compounds present in tomato such as lycopene and  $\alpha$ -tocopherol commonly found in tomato are also known inhibitors of the cytokine IL-6 [29,30], a protein known to negatively affect cognition [12] and is associated with sensations of tiredness or fatigue in some studies [31,32]. Research has also established that levels of IL-6 are induced by some types of exercise and found to be elevated in blood [13]. It is therefore possible that these compounds acting as an IL-6 antagonist may at least in part explain some observed effects. There are however many different molecules present within edible tomato fruit; Tomato is a rich source of bioavailable metabolites, containing quantitative trait locus (QTLs) for a diverse range of health-related molecules, as well as molecular signatures for some 2000 compounds with a likely broad diversity of biological activity [33]. It is plausible that different metabolites present within this fruit may be exerting a beneficial effect via a number of different pathways that remain to be fully explored. Unfortunately it was not possible to take blood samples. Therefore it was not possible to ascertain the levels of either markers of oxidative stress or discern impact on the activity of inflammatory proteins such as IL-6. Further research is therefore needed to fully explore the positive results observed in this study.

## Conclusion

In conclusion, this study identified that TE supplementation results in a positive and statistically significant effect on psychomotor traits, reaction times and visual attention but not visual learning skills.

## Acknowledgements

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## Declaration of Interest

Patent applications have been filed by The University of Nottingham. The trial and associated research activity was funded by Naturalea, a company specialist in the production of nutraceutical products.

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