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The Cognitive Effects of the Polyphenol Resveratrol in Young, Healthy Humans: A Review of Six Balanced Crossover, Placebo Controlled, Double Blind Trials

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Abstract

Background: Resveratrol increases cerebral blood flow (CBF) but concomitant improvements to cognitive performance are elusive and may be due to relatively underpowered analyses.

Objective: The current study combines the individual cohorts from x6 individual trials to create one larger, more powerful, sample size to assess a variety of cognitive outcomes.

Design: All trials were placebo controlled, balanced crossover, double blind designs. The combined demographics resulted in a sample size of N=166 with 112 Females and 54 Males between the ages of 18-35 years.

Results: Bonferroni corrected repeated measures ANCOVAs revealed no significant differences on x4 individual cognitive tasks. Paired samples t-tests also showed no effects following collapsing of sub-measures from these tasks into x5 global cognitive measures (Accuracy of attention, Speed of attention, Working memory, Speed of memory, Episodic memory) and the effect sizes were small for all outcomes.

Conclusions: The results of this summary paper definitively confirms that 500 mg resveratrol does not acutely improve a wide range of cognitions in healthy, 18-35 year old humans.

Keywords: Polyphenol; Resveratrol; Cognition

Abbreviations: NO, nitric oxide; CBF, cerebral blood flow; NIRS, near-infrared spectroscopy

INTRODUCTION

Resveratrol (3,4',5 trihydroxystilbene) is a phytoalexin polyphenol with over 20 thousand research papers dedicated to its investigation. The relative abundance of research into this polyphenol is likely due to the multifarious mechanisms that it is able to interact with. Anti-inflammatory effects have been observed in humans alongside reductions in nuclear factor kappa β (NF- κβ) cells [1], and antioxidant, phytoestrogen and cardiovascular effects are reported following interaction with nuclear factor erythroid 2 (Nrf2), oestrogen receptors α and β and with platelet aggregation respectively [2]. Given the prolific bioactivity of resveratrol and, of interest here, the fact that all of the above relate directly or indirectly to brain function, it is surprising that a greater proportion of the abovementioned research interest is not dedicated to central nervous system (CNS) effects in humans and the ensuing behavioural outcomes. Only 64 of the abovementioned 20 thousand papers pertain to humans and only 4 of these were direct investigations of cognition .

One such promising CNS interaction which has received some research attention here is with regards blood flow and perfusion. In this respect it has been shown that resveratrol beneficially modulates platelet aggregation [3], and platelet nitric oxide (NO) synthesis [4] and enhances endothelium-dependent [5] vaso-relaxation by promoting endothelial NO synthase (eNOS) and/or NO synthesis. In humans, resveratrol supplementation produces a dose-response increase in peripheral blood flow. For example, only an hour following consumption, resveratrol increases perfusion to the brachial artery, as measured via flow-mediated-dilatation (FMD), in overweight/obese middle-aged men and

women [6].

These blood flow enhancements also extend to the brain where recent studies report dose-response increases in cerebral blood flow (CBF) in older adults with type II diabetes [7]; and, by the same research group, that this can extend to improvements in overall cognition, specifically targeting verbal memory, in post-menopausal women following 14 weeks supplementation of a 75 mg dose [8]. The hypothesis that cognitive enhancements should follow this increased fuel provision to neural tissue is not one which is widely supported however. Research over the past decade, the majority by our own lab, has repeatedly observed robust CBF increases; typically between 45-90 minutes post-consumption of a 500 mg dose, but little in the way of cognitive enhancement. The nine trials that we have conducted over the last ten years have evinced few significant cognitive effects despite adapting the initial paradigm [9] to be more cognitively demanding [10], to increase the plasma bioavailability of resveratrol with piperine [11], to investigate chronic consumption [12], utilize more expansive cognitive tasks with a larger sample size [9], inhibit the potentially close to ceiling performance of the young (18-35 years), healthy cohorts utilizing hypoxia [13, 14] and to investigate healthy, older (aged 50-70 years) adults [15]. Four of these trials have evinced cognitive effects and when viewed in isolation these effects could simply be type I errors but, when considered as a whole, could simply be the product of underpowered analyses failing to detect true, albeit potentially subtle, effects.

Due to various practical limitations, the above-mentioned nine trials were conducted with sample sizes of between 22-46 participants and, whilst this appears adequate to detect changes in CBF, the more capricious changes to cognition likely require greater power to detect. In support, the above trial by Wong revealed clear CBF effects with only 36 participants but cognitive effects were only observed when the cohort reached N=80 in the later Evans trial. Of course differences in the cohort demographics could be responsible here; with the estrogenic effects of resveratrol more impactful on cognition in the post-menopausal women of the latter trial. However, the failure to observe cognitive effects in the face of CBF enhancement is one which is seen with other polyphenols too and may suggest that compromising statistical power to accommodate the measurement of CBF (with practical limitations of neuroimaging often restricting sample size) is likely to reduce the opportunity to detect cognitive effects.

As an example, cocoa polyphenols demonstrate robust CBF effects with relatively small samples; e.g. Sorond et al [16] report increased middle cerebral artery (MCA) perfusion in N=34 healthy elderly participants following 1- and 2 weeks of 900 mg/ day cocoa flavanols. Cocoa polyphenols are also capable of some very convincing effects on cognition with larger sample sizes; e.g. both Desideri et al [17] and Mastroiacovo et al [18] report faster performance on the Trail Maker Task (TMT) and better verbal fluency in groups of N=90 mild cognitive impairment (MCI) and healthy, respectively, elderly participants following 8 weeks of 990- and 520 mg/ day cocoa flavanols. However, when aiming to measure cognition in the reduced sample sizes dictated by neuroimaging, these effects are lost; e.g. Francis et al. [19] find significantly stronger blood oxygen level dependent (BOLD) responses during cognitive performance in N=16, 18-30 yr olds following 5 days of 150 mg/ day cocoa flavanols, but no effects on performance of the tasks themselves.

The need for more powerful cognitive analyses in polyphenol trials is clear. However, a cursory glance at these trials reveals huge variety in methodologies; with vastly differing cohorts, cognitive tasks and dosing regimens to name just a few. We would, therefore, argue that meta-analytical investigations of the resveratrol and cognition literature are not currently feasible. This assertion is supported by a recent meta-analysis of ten appropriate trials [20] where only three reported any significant effects and, further, the interpretation of two of these is muddied by the co-supplementation of red wine and quercetin to resveratrol. However, a first step at determining whether/where resveratrol is capable of evincing cognitive enhancement in humans may be to review the trials conducted only by our own lab. Over the past decade a key polyphenol research stream has provided nine resveratrol intervention trials in healthy adults with methodological variables consistent between six; here the cognitive tasks used, the demographics of the participants and the post-dose testing timeframe are equivalent but, whilst CBF effects were consistent across all, only a smattering of cognitive improvements were observed within three of the studies and this may be due to the small sample sizes (between N=22-46) used. The aim of the current study, therefore, is to combine the data from these six trials into a single more powerful analysis of a range of cognitive domains in young, healthy adults.

METHODS

Study Design and Participants

Out of the nine trials, six adopted a repeated measures, balanced cross-over design and included 500 mg trans-resveratrol as one of the investigational doses in participants aged 18-35 years. This resulted in a combined sample of 166 participants

(54 male; 112 female). Table 1 displays summary information for each individual trial and assigns a number to each for ease of reference from here on in. All trials were crossover paradigms and placebo controlled, double blind and counterbalanced via Latin square. For all trials, participants attended the laboratory in the morning having had nothing to eat or drink (except water) since the previous evening, and no resveratrol containing products for 24 hours.

All participants reported themselves to be in good health and free from social drugs, alcohol, prescription medication and herbal extracts/food supplements. Participants who had suffered a head injury, neurological disorder or neuro-developmental disorder were excluded from participation, as were those who had any relevant food allergies or intolerances, smoked tobacco, drank excessive amounts of caffeine (more than 6 cups of coffee per day) or took illicit social drugs.

Table 1: Summary of trails incorporated into review. All trails were conducted between 2008-2017 to good clinical practice standard and all assessed 500 mg resveratrol as at least one of the doses under investigation. All trails were cross-over investigations and all were balanced, placebo-controlled and double-blind. Data from trial numbers 3 and 6 was published as part of a PhD thesis only [9], study 1 has been submitted for publication and studies 2 and 4 are intended for submission for publication in the coming months. Therefore, the methodologies for all three latter studies can be found within supplementary materials.

Study reference number	Reference and Clinical Trials ID	Summary of design	Participant demographics	Post-dose time-frame and number of merged task repetitions	Cognitive findings	Additional information
1	Wightman et al. (submitted) NCT03100019	The cognitive, mood and cerebral blood flow effects of 500 mg resveratrol at sea level and during hypoxia (equivalent to ~2000 m above sea-level	N=23 (9M, 14F; 18-34 years)	45-90 minutes (3)	Significantly fewer errors on combined serial 3s and 7s subtractions	Used sea-level data only
2	Eschle et al. (In prep) NCT03541993	The cognitive, mood and cerebral blood flow effects of 500 mg resveratrol at sea level and during hypoxia (equivalent to ~4000 m above sea-level	N=24 (8M, 16F; 19-33 years)	45-90 minutes (3)	Significantly increased serial 3s subtraction accuracy and choice reaction time speed	Used sea-level data only
3	Wightman et al. (2014)	Investigation into the cognitive and mood effects of 500 mg resveratrol	N=46 (10M, 36F; 18-22 years)	40-70 minutes (1)	None	Study also included 2nd, 3rd and 4th post-dose task repetitions at 2.5-, 4- and 6 hours post-dose respectively which were not used here
4	Eschle et al. (In prep) NCT03546075	The effects of 250- and 500 mg resveratrol on whole body metabolism during high cognitive demand	N=27 (15M, 12F; 18-35 years)	45-55 minutes (1)	None	Study also included 2nd and 3rd post-dose task repetitions at 2- and 3 hours post-dose which were not used here. Only 500 mg resveratrol data was used here.
5	Kennedy et al. (2010) NCT01010009	Assessing the acute effects of 250- and 500 mg resveratrol on cognition and cerebral blood flow. Plasma bioavailability of resveratrol was assessed in a separate group of 9 males	N=22 (3M, 19F; 18-25 years)	45-85 minutes (4)	None	Only 500 mg resveratrol data was used here
6	Wightman et al. (2014)	Assessing the acute effects of 500- and 1000 mg resveratrol on cognition and cerebral blood flow	N=24 (10M, 14F; 18-35 years)	90-100 minutes (1)	Significantly increased serial 3s subtraction and rapid visual information processing accuracy	Study comprised x6 post-dose task repetitions between 90-150 minutes post-dose but only the first repetition is used here. Only 500 mg resveratrol data was used here

Treatments

All trials administered 500 mg as at least one of the doses of interest and this was via x2 vegetarian capsules administered double blind. Studies 5 and 6 all utilized Transmax trans-resveratrol from Biotivia Bioceuticals (Vienna, Austria). Studies 1, 2, 3 and 4 all utilized MegaResvertarol trans-resveratrol powder. The purity of both extracts (99.02- and 99.01% respectively) had been confirmed by HPLC for the manufacturer's certificate of analysis and both products are derived naturally from Polygonum Cuspidatum.

Cognitive Assessment

All cognitive function tests were delivered using the Computerised Mental Performance Assessment System (COMPASS). This testing system delivers a bespoke collection of tasks, with fully randomised parallel versions of each task delivered at each assessment for each individual. The battery has been in use within BPNRC for over 10 years and is now commercially available for other research organisations (www.cognitivetesting.co.uk) and is currently in use within a number of UK, US, New Zealand, and Australian Universities, companies and research organisations.

Cognitive Demand Battery (CDB)

The cognitive demand battery (CDB) is a collection of three tasks: 2 minutes each of Serial 3 and 7 subtractions and 5 minutes of Rapid Visual Information Processing (RVIP). This 9-minute battery has a

well validated literature; demonstrating sensitivity to the effects of a number of interventions, e.g. ginkgo biloba and ginseng [21], ginseng and glucose [22] and glucose and caffeine [23].

Serial subtractions (3s and 7s)

The serial 3s and 7s subtractions are completed consecutively with the procedure for both as follows: At the start of the 2 minute task a standard instruction screen informs the participant to count backwards in 3s or 7s as quickly and accurately as possible, using the keyboards linear number keys to enter each response. Participants are instructed verbally at the outset that if they are to make a mistake they should carry on subtracting from the new incorrect number with subsequent responses scored as correct in relation to the new number. To begin, a random starting number between 800 and 999 is presented on the computer screen, which is cleared by the entry of the first response. Each three-digit response is represented on screen by an asterisk and pressing the 'enter' key signals the end of each response and clears the three asterisks from the screen. Thus, participants are never aided by the previous number, nor the entry of the new number, existing on-screen. In terms of task outcomes, performance data for the subtraction tasks comprises number of correct and incorrect responses. Studies 2 and 5 also incorporated serial 13s and 17s subtractions.

Rapid Visual Information Processing (RVIP)

The RVIP task requires the participant to monitor a continuous series of single digits for targets of three consecutive odd or even numbers. The white digits are presented on the black computer screen at the rate of 100 per minute; with eight correct target strings in each minute presented in pseudo-random order. The participant responds to the detection of a target string by pressing the appropriate response button as quickly as possible. In terms of task outcomes, RVIP is scored for number of target strings correctly detected, the average reaction time (msec) for correct detections and the number of false alarms.

NBack (3Back version)

This task requires participants to monitor a continuous sequence of numbers presented on screen, one at a time. Participants must respond to each letter, indicating whether they had observed the letter 3 letters back in the sequence, or not, by pressing the 'yes' or 'no' button on the response box as quickly as they can. This task is completed for 2 minutes and is scored for percentage accuracy and reaction time (msec).

Choice Reaction Time

The CRT task requires participants to indicate, by pressing the 'left' or 'right' response box button, the direction of the arrow presented on the computer screen. Fifty stimuli (arrows) are presented, with random delays, taking ~2 minutes to complete. The task is scored for percentage correct responses and reaction time (msec).

Numeric Working Memory

For this task, a set of five target numbers are presented on screen, separately, with an inter-stimulus time of 1000ms. A series of numbers are then presented to which participants must respond 'yes' or 'no' as to whether they were part of the originally presented set or not. This task is repeated three times consecutively (with different target numbers each time) and is scored for percentage correct detections and reaction time (msec).

Picture Recognition

At the beginning of each task battery a series of pictures are presented on screen, one at a time, which the participants are asked to commit to memory. At the end of the task battery, with the interim tasks also acting as distractors, the pictures are again presented on screen, one at a time, interspersed with novel/nuisance pictures. Participants must respond by pressing 'yes' or 'no' as to whether they have seen each image before or not and is scored for the number of correct detections.

Word Recognition

At the beginning of each task battery a series of words are presented on screen, one at a time, with participants requested to commit these to memory. At the end of the task battery, with the interim tasks also acting as distractors, the words are again presented on screen, one at a time, interspersed with novel/nuisance words. Participants must respond by pressing 'yes' or 'no' as to whether they have seen each word before or not and is scored for the number of correct detections.

Accuracy of Attention

This global cognitive domain is derived by combining the % correct Z scores from choice reaction time, numeric working memory and rapid visual information processing tasks.

Speed of Attention

Combines the millisecond speed of response Z scores from choice reaction time, numeric working memory and rapid visual information processing tasks.

Working Memory

Comprises the % correct Z scores for the serial 3s, 7s and 17s subtractions as well as the 3Back task.

Speed of Memory

Averages the millisecond speed Z scores for the picture and word recognition tasks.

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Episodic Memory

Averages the % correct Z scores for the picture and word recognition tasks.

Each of the six studies incorporated into this summary contains a different collection of the above tasks and so table 2 denotes which trials provide each task and the collective sample size for each analysis.

Table 2: Data analysis table. Depicting the individual tasks analysed (top portion) as well as the global cognitive domains (bottom portion) and the individual tasks which collapse into these. The table also details from which of the six trials these derive from (See table 1 to indicate which trials these numbers refer to) and the combined number of participants in each analysis.

	Task	Study	N
Cognitive Demand Battery	Serial 3 subtractions	1, 2, 3, 4, 5, 6	166
	Serial 7 subtractions	1, 2, 3, 4, 5, 6	166
	Rapid Visual Information Processing	1, 2, 3, 5, 6	139
NBack (3 Back version)		1, 3, 5	91

Global cognitive domain	Task	Study	N
Accuracy Of Attention (% correct)	Choice Reaction Time	2, 3	255
	Rapid Visual Information Processing	1, 2, 3, 5, 6	
	Numeric Working Memory	3	
Speed Of Attention (msec)	Choice Reaction Time	2, 3	255
	Rapid Visual Information Processing	1, 2, 3, 5, 6	
	Numeric Working Memory	3	
Working Memory (% correct)	Serial 3 subtractions	1, 2, 3, 4, 5, 6	450
	Serial 7 subtractions	1, 2, 3, 4, 5, 6	
	Serial 17 subtractions	4	
	N(3)Back	1, 3, 5	
Speed Of Memory (msec)	Picture Recognition	3	139
	Word Recognition	1, 2, 3	
Episodic Memory (% correct)	Picture Recognition	3	139
	Word Recognition	1, 2, 3	

Procedure

All trials comprised an initial training/ screening visit which was followed within 2-14 days by the first testing visit. All testing visits were conducted in the morning and began with at least 1 baseline repetition of the cognitive task battery under investigation and all but studies 3 and 6 then began post-dose cognitive testing 45 minutes following consumption of 500 mg resveratrol. Study 3 began at 40 minutes post-dose and study 6 at 90 minutes. The trials varied in the number of post-dose task repetitions utilized and so this review will average performance on each measure across post-dose repetitions; with this data collected between 40-100 minutes post-dose. Studies 3, 4 and 6 also collected data beyond this point but, in order to keep the window of post-dose testing equal across the trials, this data was not used here. Finally, studies 1 and 2 comprised x4 testing sessions where testing of the placebo and resveratrol doses was conducted both at sea level and at ~2000- and 4,000 m above sea level respectively. To ensure equitability of the studies used in this review, only the sea level data for these trials was utilized here. The diagrams depicting the testing day timeline for each trial are included as supplementary materials.

Statistics

A G*Power [24] calculation determined that to achieve a medium effect size, with 2 groups, utilizing the following analysis plan, would require a sample size of N=54 for the ANCOVA analyses and N=27 for the t-tests.

The sample sizes in the individual 6 trials provided sufficient power to analyse 4 tasks individually (Serial 3s and 7s subtractions, RVIP and 3Back) as well as to collapse appropriate task sub-measures into 5 global cognitive domains (Accuracy of attention, Speed of attention, Working memory, Speed of memory, Episodic memory). These were analysed via Bonferroni corrected repeated measures ANCOVAs with 95% confidence intervals; comparing placebo and 500 mg resveratrol whilst utilizing the study number as a covariate. This was in order to control for potential cohort effects from individual trials. In order to determine effect sizes, due to the variability in the standard deviation between treatment groups, Glass' Δ was utilized.

A secondary investigative interest of this paper was whether the boosting effects of resveratrol on CBF correlated with cognitive function. Four trials fitted the criteria for this analysis; 1, 2 and 5 as well as an additional trial [12] which assessed both the

acute and chronic cognitive and CBF effects of resveratrol; only the acute data was used here. All four trials included both placebo and 500 mg resveratrol conditions and employed the Serial 7s and RVIP tasks. Three of the studies also employed the Serial 3s task. Within-condition correlations were conducted between the change (from pre-treatment baseline) in CBF parameters during the first post-dose repetitions of these Serial 3s, Serial 7s and RVIP tasks. An additional correlation between the average change in CBF parameters across these tasks and performance on the task outcomes was also conducted.

RESULTS

Table 3 displays the results of all abovementioned cognitive analyses. All results were non-significant with effect sizes ranging Δ .01- .25; indicating negligible-small effect sizes.

Table 3: Cognitive results table. The change-from-baseline means and standard deviations for placebo and 500 mg trans-resveratrol. The table depicts the number of data points per analysis and the results of the repeated measures ANCOVA analyses (individual cognitive tasks) and paired samples t-tests (global cognitive domains) as well as an estimate of the size of these effects utilizing Glass's Δ

	Placebo			**500 mg trans-resveratrol**		**ANCOVA**		**Effect size**
Cognitive task	N	μ	SD	μ	SD	F	P	Δ
Serial 3s correct	166	2.8	10.3	2.9	7.1	.12	.73	.01
Serial 3s errors	166	.52	2.6	.37	3.0	.07	.93	.06
Serial 7s correct	166	3.1	6.5	3.0	6.3	1.0	.32	.02
Serial 7s errors	166	-.22	4.1	-.11	2.6	.00	.96	.03
RVIP correct	139	-.85	13.7	-.55	12.4	.09	.76	.02
RVIP reaction time	139	9.9	47.0	-2.0	44.8	1.6	.21	.25
RVIP false alarms	139	.08	2.2	.16	3.5	.56	.46	.04
3Back correct	91	.62	7.5	.17	5.6	.16	.69	.06
3Back reaction time	91	-109.9	210.2	-98.3	250.5	.06	.82	.06
t-test								
Global cognitive measure	**N**	**μ**	**SD**	**μ**	**SD**	**t**	**P**	**Δ**
Accuracy of attention	255	-.38	10.4	-.67	9.3	.31	.76	.03
Speed of attention	255	6.9	129.3	-4.9	66.2	1.3	.20	.09
Working memory	450	2.5	8.4	1.8	6.8	1.3	.18	.08
Speed of memory	139	13.7	142.7	14.8	132.5	.08	.94	.01
Episodic memory	139	-3.0	9.1	-3.2	8.2	.22	.83	.02

Table 4 displays the results of the Pearson's correlations between cognitive performance and CBF in response to treatment. These reveal that increases in deoxygenated haemoglobin significantly correlated with Serial 3 subtraction task performance after placebo for both total completed subtractions (r = .29, p <.001) and number of correct subtractions (r = .30, p <.001). For 500 mg resveratrol, significant correlations between increases in oxygenated and total haemoglobin and RVIP false alarm performance was observed (both r = .26, <.001).

Table 4: Correlations between cognition and cerebral blood flow. The change-from-baseline Pearson's correlations between cognitive performance and cerebral blood flow (CBF (O2-Hb; oxygenated haemoglobin, HHb; deoxygenated haemoglobin, tHb; total haemoglobin)), for placebo and 500 mg resveratrol, on the Serial 3s, 7s and Rapid Visual Information Processing (RVIP) tasks. Significant correlations are depicted in bold and all correlations were significant at the <.001 level.

		Task outcome	**No. pairs**	**Change in CBF parameter during task**			**Average change in CBF parameter across tasks**		
				O2-Hb	**HHb**	**tHb**	**O2-Hb**	**HHb**	**tHb**
placebo	Serial 3s	Total (No.)		0.06	0.29	0.14	0.04	0.32	0.14
		Correct (No.)	67	0.07	0.30	0.16	0.06	0.33	0.16
		Errors (No.)		-0.06	-0.17	-0.11	-0.07	-0.18	-0.12
	Serial 7s	Total (No.)		-0.13	-0.04	-0.13	-0.08	-0.09	-0.10
		Correct (No.)	84	-0.13	-0.07	-0.13	-0.08	-0.10	-0.10
		Errors (No.)		0.05	0.07	0.06	0.03	0.05	0.04
	RVIP	Correct (%)		-0.06	0.05	-0.03	-0.03	0.02	-0.02
		RT (msecs)	84	-0.07	0.20	0.01	-0.16	0.10	-0.11
		False alarms (No.)		-0.08	-0.08	-0.10	-0.11	-0.12	-0.14
500 mg resveratrol	Serial 3s	Total (No.)		-0.09	0.03	-0.06	-0.09	0.03	-0.07
		Correct (No.)	67	-0.08	0.09	-0.04	-0.07	0.08	-0.03
		Errors (No.)		0.00	-0.13	-0.04	-0.03	-0.12	-0.06
	Serial 7s	Total (No.)		0.01	0.13	0.05	0.02	0.12	0.05
		Correct (No.)	84	0.00	0.10	0.03	0.01	0.08	0.03
		Errors (No.)		0.03	0.02	0.03	0.02	0.04	0.03
	RVIP	Correct (%)		0.05	-0.03	0.03	0.05	-0.04	0.03
		RT (msecs)	84	0.04	0.13	0.07	0.07	0.10	0.08
		False alarms (No.)		-0.26	-0.18	-0.26	-0.28	-0.14	-0.27

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DISCUSSION

The aim of the current paper was to answer a research question which has been a focus for our lab over the past decade; does resveratrol improve cognitive function acutely in healthy, young humans? The results of nine (six of which were sufficiently methodologically similar to include in this review) individual trials during this time were unable to clarify this question and one argument levied against these trials was that underpowered analyses may have been masking effects. Because the resveratrol (and wider phenolic) literature regarding cognition is still relatively small, and methodologically heterogeneous, a factor analysis proper of the wider literature is, arguably, not possible. This is supported by a recent meta-analysis which reports unconvincing cognitive effects (limited to delayed word recognition) from 3/10 trials and so clearly pooling the individual effects from these heterogeneous trials has not clarified the issue. However, the six abovementioned trials that our individual lab has conducted were all designed with equivalent cohorts, measurement periods, cognitive assessments and all utilized 500 mg trans resveratrol. As such, rather than a traditional factor analysis, the current paper reports the results of the combined data from these trials; covarying the trial number in order to protect against potential cohort or time effects.

The results here quite definitively confirm that 500 mg resveratrol is not capable of producing convincing acute cognitive improvements in young, healthy adults. By extension, the findings here also retrospectively suggests that the smattering of cognitive effects seen in the individual three/ six trials are more likely to represent type I errors, potentially due to the inclusion of task repetition as a factor , rather than small effects being masked by too small sample sizes. The inflation of sample size here brings with it an almost complete lack of any effects and negligible effect sizes.

Whilst the authors of this paper are confident in interpreting the above as null effects of resveratrol in this specific model, the argument could be levied that the combination of these six trials does not represent sufficient evidence to make such a bold statement. For example, one could argue that other cognitive tasks may be more sensitive to the acute effects of this dose of resveratrol or that the post-dose measurement period may not be capturing the most active period of resveratrol. It is certainly possible that another task/ s may be more appropriate to utilize with resveratrol, and indeed other polyphenols; but the individual tasks analysed here have proven sensitivity, in a similar paradigm, with cocoa polyphenols previously [25] and the inclusion of the five global cognitive domains, together, provides an expansive picture of overall cognition. As such, it would be difficult to identify a hitherto unexplored aspect of cognition with resveratrol.

Secondly, it is of course also possible that a more suitable window of activity, outside of the 45-100 minutes post-dose which was measured here, exists with resveratrol. However, pharmacokinetic data demonstrates that plasma resveratrol metabolites are present during this period [10] and this period of time also coincides with other measurable actions of resveratrol. Specifically, during this window, we have reported robust effects of 500 mg resveratrol on CBF parameters [10, 12] and it is this mechanism which ourselves, and other labs investigating the effects of polyphenols in humans, have attempted to associate with cognition; due to the increased provision of oxygen and glucose that it should confer to neural cells. However, the null results presented here; the product of combining the generally null/ unconvincing cognitive data from such positive CBF trials, suggests that CBF is not a viable mechanism to boost cognition in this young, healthy demographic.

As noted in the introduction, this is a story which is mirrored with other polyphenols; e.g. cocoa flavanols, where positive findings are reported with different (i.e. not young and healthy) demographic groups and alternative mechanisms attributed. For example, Desideri et al. [17] and Mastroiacovo et al. [18] report equivalent significant improvements in motor and verbal function in elderly adults following cocoa polyphenol consumption and, in both cases (the former in those with MCI and the latter without), insulin sensitivity was improved and explained a high proportion of the variance in the cognitive improvements. In post-menopausal women, Evans et al. [8] did report improvements in verbal memory and 'overall cognition' alongside increased cerebrovascular responsiveness after resveratrol but this was not accompanied by increases in CBF. These effects are therefore more likely the result of the phytoestrogen activity of resveratrol [26]; with oestrogen replacement shown to improve cholinergic function in brain regions key to learning, memory and attention in animal models [27]. Whilst the estrogenic activity of resveratrol hasn't been directly investigated with regards cognition in humans, other polyphenols demonstrating estrogenic activity, e.g. isoflavones from soy, have translated this biological activity into improved cognitive function, specifically verbal memory [28].

Taken together, the evidence suggests that resveratrol, and related polyphenols like those from

cocoa, may have the greatest promise cognitively in older participants with some aspect of compromise; e.g. related to insulin insensitivity and oestrogen depletion, and that these may serve as more convincing mechanisms underpinning cognitive function than CBF. This is supported by the additional findings of this paper; that changes in CBF did not correlate with cognitive performance. Here, only false alarms on the RVIP task evinced any significant change (on oxygenated and total haemoglobin levels) following resveratrol consumption and placebo consumption was associated with more effects; correlating increases in deoxygenated haemoglobin with x2 measures of performance on the Serial 3 subtraction task.

It should also be noted that all of the abovementioned trials which revealed cognitive improvements following resveratrol and cocoa polyphenols in these compromised groups were the product of chronic dosing regimens; between 8-14 weeks, and this also likely contributes to the positive effects reported. Finally, whilst this message could be perceived negatively it should be made clear that the null effects of resveratrol reported here are restricted to the specific model of acute intervention with young (18-35 years), healthy humans who are predominantly undergraduate students. Further, the positive effects of resveratrol reported with other models confirms that resveratrol is capable of clear and robust effects and, together, this helps focus the future research direction into these areas rather than with the young and healthy.

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