JUVENESCENCE®

THE SCIENCE BEHIND Cognitive Switch®

A White Paper from Juvenescence®
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Introduction

The Juvenescence team is proud to offer an exciting new beverage to support brain health and cognitive function. We began our journey a couple of years ago with the product, Metabolic Switch® ketone fuel. The Chocolate Nitro drink and Unflavored powder worked great for elevating ketones but tasted terrible. Our team focused on improving taste, which has resulted in a new ketone di-ester that you will enjoy drinking, and created a whole new product experience that we call Cognitive Switch® beverages (ready to drink, powder base).

There is one functional area that stands out in the crowd of published research on ketones. That area is cognition. As the key backup evolutionary brain fuel, exogenous ketones are a powerful tool in the modern toolbox for promoting and supporting brain energy. There are many limitations to the current methods for raising ketones — unsustainable restrictive diets, high salt load, highly acidic solutions, and oils that taste bad or aren't tolerated very well. With Cognitive Switch® beverages, we set out to address all of these limitations and create a solution that could be embraced without these tradeoffs.

We present to you the science behind Cognitive Switch® beverages.

Purpose

This white paper seeks to share our process for summarizing the brain health and cognition clinical work that underpins the science behind the product.

Background

Beta-hydroxybutyrate (BHB) is one of the three physiological "ketone bodies" produced endogenously from fatty acids in the setting of a ketogenic diet [1], starvation [2], or following strenuous exercise [3, 4]. In modern humans consuming a mixed diet containing significant carbohydrate, BHB levels are typically low (< 0.1 mM). During periods of prolonged carbohydrate restriction, BHB levels in the blood increase, and physiological nutritional ketosis develops (BHB ≥ 0.5 mM) [1, 5-7]. Pathological ketoacidosis (blood BHB > 10 mM) occurs in dysregulated metabolic states such as Type 1 Diabetes Mellitus [5]. During physiological ketosis, BHB functions as a metabolic fuel to facilitate ATP generation [8], particularly in the **brain**, heart, and skeletal muscle. Additionally, growing evidence suggests that BHB acts as a signaling metabolite, directly and indirectly modulating receptor activation and gene expression, which ultimately could impact lifespan and healthspan.

Endogenous ketosis involves lipolysis to generate fatty acid substrate for the liver, hepatic ketogenesis, hyperketonemia, and increased ketone oxidation [9]. Recently, exogenous sources of ketones, such as ketone esters, have been developed for their ability to elevate blood ketone concentrations without the need for changes in dietary macronutrient intake. Ketone esters have been used to test the effects of exogenous ketosis on a variety of endpoints across states of health and disease, ranging from physical [10-13] and cognitive performance [14-16] to blood glucose regulation [17-20] and cardiac function [21, 22].

C8 ketone di-ester (chemical name: bis-octanoyl (R)-1,3-butanediol, BO-BD) is the novel ketone ester in Cognitive Switch® beverages that induces hepatic ketogenesis and elevates circulating ketone concentrations independently of dietary carbohydrate intake or circulating insulin concentrations. Oral administration of C8 ketone di-ester in humans results in a state of nutritional ketosis that lasts up to several hours [23, 24]. C8 ketone di-ester is rapidly hydrolyzed in the small intestine to form the ketogenic precursors (R)-1,3-butanediol and two moieties of the medium chain fatty acid octanoic acid (C8). Octanoic acid and (R)-1,3-butanediol are transported to the liver via the portal circulation where octanoic acid acts as a constitutive substrate for "classical" hepatic ketogenesis [25], and butanediol is converted to BHB via a "non-classical" hepatic ketogenic pathway [26,27] (**Figure 1**). C8 ketone di-ester is self-affirmed Generally Recognized as Safe (GRAS) for use as an ingredient in beverages.

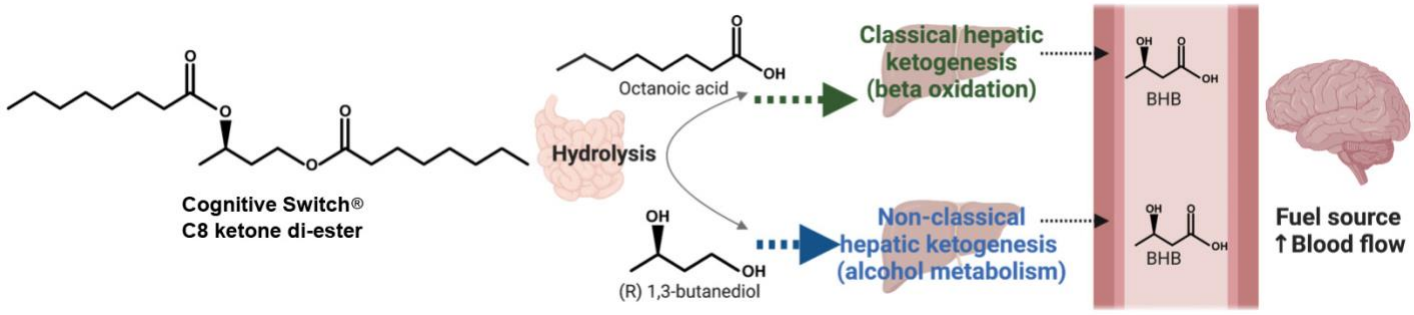

Figure 1. *Schematic illustrating metabolic pathways involves in endogenous ketosis and exogenous ketosis following C8 ketone di-ester ingestion. Created with BioRender.*

Approach

For Cognitive Switch® beverages, we based our cognition messaging substantiation on a process we call "totality of the clinical evidence" assessment. We focused on clinical research as opposed to extrapolating from animal or cell models. We conducted a search for studies that might relate to our product and removed those that were not in consumer-relevant populations (i.e., in disease populations) and those that didn't use doses or serving sizes that are comparable to what is delivered in our product. Then we examined all remaining studies. This white paper takes you through our substantiation process step by step.

Step 1: PubMed Search

In early 2023, a PubMed search was conducted to find published clinical studies with cognitive and brain health-related outcomes in the area of exogenous ketones and the ketogenic diet. Cognitive Switch® drink and powder are food products, so for the purposes of summarizing the evidence, disease populations (e.g., mild cognitive impairment, Alzheimer's disease) were excluded. The target population for Cognitive Switch® drink and powder is healthy adults and the product is not intended to treat, prevent, or mitigate any diseases.

Twenty-five studies were evaluated following a PubMed search for publications that tested the effect of ketosis on the brain. The following test substances were considered relevant because they are all ways to raise circulating ketone bodies, as measured by blood beta-hydroxybutyrate (BHB).

- Ketone monoester (KME; BHB-BD)

- Oral beta-hydroxybutyrate salts (BHB salt)
- Medium chain triglycerides (MCT)
- Intravenous (IV)-BHB salt infusions
- Ketogenic diet

In September 2023, we noted the recent publication of a compelling large study by Sae-jie et al [28] that included observational data (n = 5506 subjects) and Mendelian randomization analysis (n = 257,841 subjects) to conclude that BHB concentrations were positively associated with general cognitive function (observational data) and further that BHB was protective for cognitive performance (Mendelian randomization data). Whilst this study did not examine exogenous ketone products, it provides strong support for a cognitive effect of BHB.

Step 2: Sort all studies by intervention and determine if dose OR ketone concentration is relevant

Table 1 lists the number of studies (n) from each type of ketogenic intervention that also reported outcomes relevant to cognition and brain health. In the far-right column of Table 1, we applied an initial filter to retain only those studies where the dose (serving size studied) of ketone or ketone precursor is relevant to the recommended serving size of Cognitive Switch® beverages OR where the reported ketone concentration is comparable to that achieved from recommended consumption of Cognitive Switch® beverages. Each serving of Cognitive Switch® drink or powder contains 12.5 g of C8 ketone di-ester and 1–2 servings increases blood BHB to 0.8–1.6 mM[24].

Table 1 – Intervention for Inducing Ketosis and Dose Relevance in 25 Studies Evaluated

Intervention	Number of Studies (n)	Studies (n) Where Dose is Relevant to 12.5 g/serving and/or 25 g/day of Cognitive Switch® beverage
Ketone monoester (KME; BHB-BD)	8	2
MCTs	8	8
IV-BHB salts	4	3
Oral BHB salts	3	0*
MCT + BHB salts	1	1
Ketogenic diet	1	0**
Total		**14**
Abbreviations: BHB = beta-hydroxybutyrate, BHB-BD = beta-hydroxybutyrate esterified to butanediol, IV = intravenous, KME = ketone monoester, MCT = medium chain triglycerides		

*Doses and degree of ketosis achieved were lower than that of recommended serving of C8 ketone di-ester.

**Level of ketosis achieved by diet exceeded that which is observed from use of C8 ketone di-ester in recommended amounts.

Among the 14 studies where doses were relevant and/or achievement of ketosis was comparable to the recommended use of Cognitive Switch® drink and powder, 6 studies represented non-acute or longer-term interventions (N = 5 with medium chain triglycerides (MCT), N = 1 with ketone monoester).

Step 3: For dose-relevant studies, summarize if top-line results support an effect of ketones on the brain

Top-line results (favorable vs. unfavorable) of the 14 relevant studies are summarized in Table 2. For efficacy domain, "cognition" is used for measurements of executive function, processing speed, working memory, and

other outcomes measured for the purpose of evaluating cognitive endpoints. The term "brain" under domain refers to demonstration of efficacy in brain blood flow, fuel utilization, or other non-cognitive endpoints involving the brain.

Table 2 – High Level Summary of Results from 14 Studies Where Dosing Was Relevant to Recommended Intake of Cognitive Switch® Drink

Author, Year	Active	Peak [BHB] (mM)	Time Course	Domain	Favorable Outcome?
Abe, 2017 [29]	MCT	ND	Longer term	Cognition	Yes
Abe, 2020 [30]	MCT	ND	Longer term	Cognition	Yes
Ashton, 2020 [31]	MCT	ND	Longer term	Cognition	Yes
Jensen, 2020 [32]	BHB-IV	2.4	Acute	Cognition	Yes
Mikkelsen, 2014 [33]	BHB-IV	0.5, 0.75, 1.75	Acute	Brain (Fuel)	Yes
Mutoh, 2022 [34]	MCT	ND	Longer term	Cognition (**Brain**)	No (**Yes**)
O'Neil, 2019 [35]	MCT	0.1, 0.5, 0.5, 0.6	Longer term	Cognition	No
Ota, 2016 [36]	MCT	0.5	Acute	Cognition	Yes
Page, 2019 [37]	MCT	0.4	Acute	Cognition	Yes
Prins, 2020 [38]	BHB+MCT	0.7	Acute	Cognition	Yes
Quinones, 2022 [39]	KME	1.7	Acute	Cognition	Yes
Veneman, 1994 [40]	BHB-IV	1.7	Acute	Cognition	Yes
Walsh, 2021 [41]	KME	1.8	Longer term	Cognition, Brain	Yes
Yomogida, 2021 [42]	MCT	0.6*	Acute	Cognition, Brain	Yes
Abbreviations: BHB = beta-hydroxybutyrate, IV = intravenous, KME = ketone monoester, MCT = medium chain triglycerides, ND = not detected.					

* total ketone concentration

Among the 14 studies summarized in Table 2, two reported no effect on cognition. The Mutoh study (2022) randomized 63 healthy, normal elderly adults (male and female) to either 18 g/d of MCT oil or matching placebo (double-blind) for 3 months. Assessments before and after intervention included 6-min walk test, cognition, brain focal glucose metabolism by ^{18}F-fluorodeocyglucose positron emission tomography, and magnetic resonance imaging-based functional connectivity. The MCT group did not show any difference in cognitive parameters measured but did show significant improvement in balance ability, suppressed glucose metabolism in right sensorimotor cortex, and increased functional connectivity in brain. While this paper does not support improved cognition for this intervention, it does lend relevant support to ketone bodies fueling the brain and improving non-cognitive brain endpoints.

The O'Neil study (2019) randomized 80 healthy older adults (male and female) to either 30g/d of MCT oil or matching placebo (double blind) for 14 days. Assessments before and after the intervention consisted of the Cambridge Neuropsychological Test Automated Battery (CANTAB: paired associates learning, verbal recognition memory, spatial working memory, rapid visual processing, and reaction time). The MCT group did not show difference in cognitive parameters; the authors note in the discussion that the mean plasma BHB concentrations during the testing sessions (0.28 and 0.29 mM) were lower than those seen in positive studies and are substantially lower than seen with consumption of Cognitive Switch® at recommended servings sizes [24].

Step 4: For dose-relevant and supportive studies, determine if they are relevant to our target consumer

For the supportive studies (N = 13), a closer evaluation at the study population and any cognitive stressors that were applied as part of the research protocols are summarized in Table 3.

Table 3 – Study Populations and Relevance to Target Consumer (Healthy Adults)

Study	Subjects	Cognitive Stressor	Assessment of Relevance to Target Consumer
Abe, 2017 [29]	N = 38 frail elderly adults, mean age ~86 y	Frailty, age	Relevant to healthy adults
Abe, 2020 [30]	N = 64 frail elderly adults, mean age 85 y	Frailty, age	Relevant to healthy adults
Ashton, 2020 [31]	N = 30 healthy young adults, mean age 20 y	None	Relevant to healthy adults
Jensen, 2020 [32]	N = 18 patients with type 2 diabetes, mean age 65 y	Diabetes is associated with glucose hypometabolism	Moderately relevant given the prevalence of diabetes in U.S. population among older adults
Mikkelsen, 2014 [33]	N = 6 healthy male volunteers, mean age 23 y	None	Relevant to healthy adults
Mutoh, 2022 [34]	N = 65 healthy older adults, mean age ~70 y	None	Relevant to healthy adults
Ota, 2016 [36]	N = 19 cognitively fit older adults, mean age 66 y	None	Relevant to healthy adults
Page, 2019 [37]	N = 11 patients with type 1 diabetes	Hypoglycemia (from 5.5 mM to ~2.8 mM)	Severe hypoglycemic stressor likely not relevant to target audience
Prins, 2020 [38]	N = 13 recreational male runners, mean age ~25 y	5 km run	Relevant to healthy adults
Quinones, 2022 [39]	N = 9 recreationally active men, mean age 30 y	40 minute mentally fatiguing task	Relevant to healthy adults
Veneman, 1994 [40]	N = 13 healthy volunteers, mean age 34 y	Hypoglycemia (from 5.2 mM to ~2.2 mM)	Severe hypoglycemic stressor likely not relevant to target audience
Walsh, 2021 [41]	N = subjects with BMI > 30 $kg.m^2$ or HbA1C 5.6–6.9 mM, mean age 56 y	None	Relevant to healthy adults
Yomogida, 2021 [42]	N = 20 healthy older adults, mean age 66 y	Concurrent MRI scanning	Relevant to healthy adults

Abbreviations: BMI = body mass index, km = kilometers, mM = millimolar, MRI = magnetic resonance imaging, N = number of subjects.

Step 5: For dose-relevant, supportive studies in a relevant population, evaluate strength of support

For the studies with relevant populations (N = 11), an evaluation was performed of the outcome measures and findings to determine whether the evidence supports (moderately, strongly) or does not support the use of Cognitive Switch® beverages for cognitive health, summarized in **Table 4**. Seven of the eleven studies showed a moderate or strong benefit of ketosis on brain function. Two of the eleven studies reported no benefit of ketosis for cognitive outcomes (Prins, 2020; Jensen, 2020). One study reported a benefit to cognitive endpoints but was confounded because the MCT treatment also included vitamin D3 and leucine (Abe, 2017).

Table 4 – Study Cognition-Related Outcome Measures and Findings

Study	Outcome measures	Outcome Finding	Strength of support for claims
Abe, 2017 [29]	Mini Mental State Examination (MMSE), Nishimura Geriatric (NM) Scale.	Total MMSE score ($p = 0.017$) and NM Scale score ($p < 0.001$) had a significant group x time interaction. MMSE score improved with MCT (+10.6%, $p < 0.05$), was stable with active control and decreased in PLA. The NM Scale score improved with MCT (+31%, $p < 0.001$) and decreased with active control and PLA.	**Weak-Moderate.** Multiple measures, strong statistical significance, but MCT treatment included potential confounders, leucine and vitamin D3. See Abe, 2020, which confirms result for MCT alone.
Abe, 2020 [30]	Mini Mental State Examination (MMSE), Nishimura Geriatric (NM) Scale.	Total MMSE score change over 3 mo intervention had significant group x time interaction ($p < 0.001$), MCT group had sig increased total MMSE score at 1.5 and 3 mo (and sig changes in the attention and calculation domain), whereas PLA decreased score over study. Score in MCT returned to baseline 1.5 mo post-treatment Significant group x time interaction for Total NM Scale score. Both MCT groups had improved NM scale score at 3 mo; only one group reached significance.	**Strong.** Multiple favorable outcomes.
Ashton, 2020 [31]	Trail Making Task (A and B), Digit Span (Forwards/Backwards), Spatial Span, Covert Shift of Attention, Rapid Visual Processing.	Significant group x time interaction for Trails A ($p < 0.001$; D1 improved vs. PLA at week 4, D2 improved vs. PLA at week 3 and 4, vs. D1 at week 3 and 4), Trails B ($p < 0.001$; D1 and D2 improved vs. PLA at week 3 and 4), Digit Span - Forwards ($p < 0.001$; D1 and D2 improved vs. PLA at weeks 2, 3, and 4), Digit Span - Backwards ($p < 0.001$; D1 and D2 improved vs. PLA at weeks 2, 3, and 4). No changes to other outcomes.	**Strong.** Multiple outcomes, some dose responsiveness.
Jensen, 2020 [32]	Rey Auditory Verbal Learning Test, Trail Making Test (A and B), Symbol Digit Modalities Test, Wechsler Adult Intelligence Scale, Verbal Fluency Test (S and D), Rapid Visual Processing Test (CANTAB), Danish Adult Reading Test. Global cognitive composite calculated and a composite calculated for four cognitive domains.	No effect on primary outcome of global cognitive composite, or any of the four cognitive domain composites.1.6% improvement in Weschler Adult Intelligence Scale with highly significant p value ($p < 0.001$). When multiple comparisons removed, significant improvements were seen in 3/4 domains.	**Not supportive.** NS in primary outcome. Highly significant only in one domain.
Mikkelsen, 2014 [33]	Cerebral ketone uptake	Consistent increases in cerebral ketone oxidation with increasing BHB-IV infusion rate.	**Strong.**
Mutoh, 2022 [34]	Mini Mental State Examination (MMSE), Geriatric Depression Scale, Wechsler	Sig improvement in walking balance with MCT vs. PLA ($p < 0.01$). No change in MMSE or GDS. Trails B ($p < 0.001$) and DSST ($p < 0.05$) performance significantly improved	**Moderate.** Two isolated favorable outcomes but with mechanistic support from fMRI data.

Study	Outcome measures	Outcome Finding	Strength of support for claims
	Memory Scale, Trails A and B, Digit Symbol Substitution, Wechsler Adult Intelligence Scale. fMRI imaging.	pre- to post- in MCT group, but scores were to sig different to PLA. No other cognitive differences. fMRI showed strong decrease in regional brain glucose metabolism (5-35%); correlated to improvement in balance. _	
Ota, 2016 [36]	Two time points (90 and 180 min) Wechsler Adult Intelligence Scale, Wechsler Memory Scale, Trail Making (A and B), combined to give Global Composite.	Wechsler Memory Scale (Digit Span) improved with MCT vs. PLA at 90 min ($p = 0.024$), and Trails B improved with MCT vs. PLA at 180 min ($p = 0.045$). They repeated the analysis taking the data from the timepoint where each subject had peak blood BHB; this demonstrated improvement MCT vs. PLA in Digit Span ($p = 0.042$), Trails B ($p = 0.032$) and an improved Global Composite ($p = 0.017$). They repeated the analysis separating subjects into those with low and high baseline cognitive scores; this demonstrated significant improvement of Global Composite in the low ($p = 0.005$) but not the high ($p = 0.51$) score groups. They found change in plasma BHB was correlated to improvement in Trails B score ($p = 0.045$).	**Moderate.** Whilst there are isolated effects in initial analysis, the strong and consistent effect only emerges with post hoc additional analysis.
Prins, 2020 [38]	Stroop task: reaction time, response accuracy (for both congruent and incongruent stimuli)	No significant main effect of treatment was observed for Stroop tasks while a post hoc analysis revealed some suggestion of possible effects (time by treatment interaction) that were in some cases not different from placebo or did not appear to be clinically meaningful.	**Not supportive.** The only outcome with a sig finding was NS vs. PLA.
Quinones, 2022 [39]	Stroop Task, Choice Reaction Test (CRT).	KME attenuated the exercise induced decline in CRT vs. PLA (1.3% vs. 3.4% reduction in correct answers, $p = 0.02$). No changes in Stroop.	**Weak-moderate.** Highly significant finding but only in one outcome.
Walsh, 2021 [41]	Digit Symbol Substitution Task (DSST), Stroop Task, Task Switching. Cerebral blood flow. BDNF.	DSST number of correct responses improved pre- to post- with KME (+2.7 responses, $p = 0.0003$). No difference in STROOP, or Task Switching. Significant increase in cerebral blood flow in vertebral artery ($p = 0.0001$) with KME, that correlated to improvement in DSST. No difference in BDNF.	**Moderate.** Highly significant finding but only in one outcome. Mechanistic support from blood flow changes.
Yomogida, 2021 [42]	fMRI. N-back task, Go-No Go task.	MCT significantly increased the hit rate in the N back task vs. PLA when day, sex and age were removed as co-variates ($p < 0.05$); no change in Go-No Go. Subjects with greater improvement in N-back had smaller DLPFC volume. Subsequent subgroup analysis showed those with *lower* baseline cognitive scores sig improved in Go-No Go ($p < 0.05$) with MCT, those with *higher* baseline scores sig improved in the N-back with MCT ($p < 0.05$).	**Moderate.** Cognitive improvement in one domain in the whole population analysis, both domains with a subgroup analysis. Mechanistic support from fMRI changes.

Step 6: For dose-relevant, supportive, population relevant studies: summarize the outcome measures used and specific cognitive domains that are supported.

For the studies that were moderate/strongly supportive of an effect of ketosis on the brain, seven studies reported at least one outcome measure that supported a specific cognitive benefit of nutritional ketosis, acute or longer-term, summarized in Tables 5 (grouped by study) and 6 (grouped by cognitive domain) below. The cognitive domains that were improved by nutritional ketosis included attention, speed, cognitive flexibility, and memory. In at least two instances, the observed improvement in cognitive performance was greater in subjects with lower baseline measurements (Ota, 2016; Yomogida, 2021).

Table 5 – Tests Used in Studies Reporting Ketosis Resulted in Favorable Outcomes for Cognition

Paper	Test Administered (Link)	What these measure
Abe, 2020	Mini Mental State Examination (MMSE) Mini-Mental State Examination (MMSE) - scoring, results and uses | healthdirect	MMSE – general cognitive performance (note sig change in attention/concentration domain)
Ashton, 2020	Trail Making Test Trail Making Test - NeuRA	Visual attention Task switching Visual search speed Speed of processing
Mutoh, 2022	Trail Making Test Trail Making Test - NeuRA Digit Symbol Substitution Task (DSST) Digit Symbol Substitution Test - PMC (nih.gov)	Visual attention Task switching Visual search speed Speed of processing Motor speed Attention Visuoperceptual functions
Ota, 2016	Wechsler Memory Scale (Digit Span) Cognitive Atlas Trail Making Test Trail Making Test - NeuRA	Working memory Mental manipulation Cognitive flexibility Rote memory and learning Attention Encoding Visual attention Task switching Visual search speed Speed of processing
Quinones, 2022	Choice Reaction Time Choice Reaction Time (CRT) | Cambridge Cognition	General alertness Motor speed
Walsh, 2021	Digit Symbol Substitution Task (DSST) Digit Symbol Substitution Test - PMC (nih.gov)	Motor speed Attention Visuoperceptual functions
Yomogida, 2021	n-back task Frontiers | What Does the n-Back Task Measure as We Get Older? Relations Between Working-Memory Measures and Other Cognitive Functions Across the Lifespan (frontiersin.org)	Attentional and verbal memory (n-back test) Anxiety, impulsiveness (Go-No Go task)

Paper	Test Administered (Link)	What these measure
	Go-No Go task. Go/No-go task - Free adaptable template and step-by-step guide (testable.org)	

Table 6: Results of Positive Studies Grouped by Cognitive Domains:

	Cognitive Domain	Cognitive Test	Relevant Paper	Improvement for Ketosis Intervention (p value)
	General cognition	MMSE	Abe, 2020	+3.5 points with ketosis ($p < 0.001$)
Attention/Speed	Alertness	CRT	Quinones, 2022	1.1% ($p = 0.02$)
	Motor Speed	CRT	Quinones, 2022	1.1% ($p = 0.02$)
		DSTT	Mutoh, 2022	# Symbols Pre = 12.5; Post = 14 ($p = 0.018$)
	Attention	DSTT	Walsh, 2021	+2.7 responses ($p = 0.003$)
			Mutoh, 2022	# Symbols Pre = 12.5; Post = 14 ($p = 0.018$) TA & B $p < 0.001$
		Trail Making	Ashton, 2020	Pre = 96s; Post = 77s ($p < 0.001$)
			Mutoh, 2022	Score, ketone = 9.5; CON = 8.6. ($p = 0.024$) +4.4% hit rate ($p < 0.05$)
		Wechsler Memory Scale	Ota, 2016	Score, ketone = 9.5; CON = 8.6. ($p = 0.024$)
		n-back	Yomogida, 2021	+4.4% hit rate ($p < 0.05$)
	Visuoperceptual	Trail Making	Ashton, 2020	TA & B $p < 0.001$
			Mutoh, 2022	Pre = 96s; Post = 77s ($p < 0.001$)
	Visual search speed	Trail Making	Ashton, 2020	TA & B $p < 0.001$
			Mutoh, 2022	Pre = 96s; Post = 77s ($p < 0.001$)
	Speed of processing	Trail Making	Ashton, 2020	TA & B $p < 0.001$
			Mutoh, 2022	Pre = 96s; Post = 77s ($p < 0.001$)
Flexibility	Task Switching	Trail Making	Ashton, 2020	TA & B $p < 0.001$ Pre = 96s; Post = 77s ($p < 0.001$)
			Mutoh, 2022	
	Cognitive flexibility	Wechsler Memory Scale	Ota, 2016	Score, ketone = 9.5; CON = 8.6. ($p = 0.024$)
	Mental manipulation	Wechsler Memory Scale	Ota, 2016	Score, ketone = 9.5; CON = 8.6. ($p = 0.024$)
Memory	Working memory	Wechsler Memory Scale	Ota, 2016	Score, ketone = 9.5; CON = 8.6. ($p = 0.024$)
	Rote memory	Wechsler Memory Scale	Ota, 2016	Score, ketone = 9.5; CON = 8.6. ($p = 0.024$)
	Encoding	Wechsler Memory Scale	Ota, 2016	Score, ketone = 9.5; CON = 8.6. ($p = 0.024$)

	Verbal memory	n-back	Yomogida, 2021	+4.4% hit rate ($p < 0.05$)
	Anxiety, impulsiveness	Go-No Go	Yomogida, 2021	+5% score ($p < 0.05$)

Conclusions

We followed a systematic process to ensure that we considered all the available literature on nutritional ketosis and brain function but did not include studies that did not use a comparable dose of ketone ingredient or studies that were in a population that is not relevant to our target consumer, healthy adults. This is a best practice to ensure we are weighing the evidence as opposed to selecting only those studies which support conclusions while ignoring published trials with null or negative outcomes.

Our structured review found that multiple peer-reviewed clinical studies across a wide range of populations from young to elderly, representative of healthy adults seeking to improve and/or maintain brain health and function, and ranging in duration from acute to longer-term, support a role for nutritional ketosis in cognitive function. Studies done with imaging techniques such as fMRI and PET scans provide evidence for potential mechanisms of action. The Mutoh study (2022) demonstrated BHB improved functional connectivity in the brain, the Mikkelson study (2014) showed consistent increases in ketone oxidation with increased BHB infusion, and finally the Yomogida study (2021) used fMRI to visualize brain regions responsible for cognition and provide evidence that BHB was utilized in these regions as an extra energy source.

We conclude that there is good supportive evidence for a beneficial effect of nutritional ketosis to the level delivered by Cognitive Switch® beverages on brain function in healthy adults representative of our target consumers.

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