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A double-blind, placebo-controlled, randomised-designed GABA tea study in children diagnosed with Autism Spectrum Conditions: A feasibility study

Clinical Trial Registration: ISRCTN 72571312

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Abstract

Research has shown an association with sensorimotor integration and symptomology of Autism Spectrum Conditions (ASC). Specific areas of the brain that are involved in sensorimotor integration, such as the cerebellum and basal ganglia are pathologically different in individuals with ASC in comparison to typically developing (TD) peers. These brain regions contain GABAergic inhibitory neurons that release an inhibitory neurotransmitter, γ-Aminobutyric acid (GABA). Brain GABA levels are decreased in ASC. This study explored, for the first time, the effect of introducing a non-invasive GABA substitute, in the form of GABA Oolong tea, on the sensorimotor skills, ASC profiles, anxieties and sleep of children with ASC. Nine children took part: (5 male, 4 female). Each child participated in three tea conditions: high GABA, high L-Theanine (a compound that increases GABA), tea with low GABA content as a placebo. A double blind, repeated measures design was employed. Measures were taken after each tea condition. Sensory and ASC profiles were scored using parental questionnaires. Motor skills were assessed using a gold standard coordination assessment. Sleep was monitored using an Actiwatch and anxiety measured through cortisol assays. Subjective views were sought from parents on 'best' tea. Results showed significant improvement in manual dexterity and some large individual improvements in balance, sensory responsivity, DSM-5 criteria and cortisol levels with GABA tea. Improvements were also seen in the L-Theanine condition, although were more sporadic. These results suggest that sensorimotor abilities, anxiety levels and DSM-5 symptomology of children with ASC can benefit from the administration of GABA in the form of Oolong tea.
Key words: Autism, motor coordination, sensory, sleep, anxiety, GABA, tea

1. Introduction

In 2013, changes to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) criteria for Autism Spectrum Conditions (ASC) increased the importance of atypical sensory reactivity within the diagnostic process, by accentuating the likely presence of hypo- or hyper-sensory sensitivity [1]. Moreover, during the last decade autism research has begun to focus in greater detail on the impact of these sensory differences and their association with motor coordination, in the form of sensorimotor integration, on the development and maintenance of autism symptomology [2-4]. The underlying mechanisms and causation for this link remain unknown and in this respect research is still very much in its infancy. However, it is understood that there are specific areas of the brain that are highly involved in sensorimotor processing and integration, such as the cerebellum and basal ganglia [5-8]. It is also evident that these areas of the brain are pathologically different in individuals with ASC in comparison to typically developing (TD) peers, such as reductions in size of the cerebellum [9-10] and basal ganglia [11] and a reduction in the number of Purkinje cells; large inhibitory neurons thought to regulate motor function [12-14]. More specifically, both of these brain regions also contain GABAergic inhibitory neurons. The main inhibitory neurotransmitter, GABA (γ-Aminobutyric acid), released by these neurons, plays an important role in sensory discrimination [15]. However, GABA levels have been shown to be lower in the auditory and motor cortices of children with ASC [16]. Furthermore, GABAergic neurons are also present in the amygdala, which is thought to have a crucial part in emotion processing [17]. This apparent deficiency of GABA within the ASC brain could have a global impact on sensorimotor skills and emotion processing, which are both impaired in ASC. This study is novel in aiming to explore the effect of introducing a non-invasive GABA substitute, in the form of GABA Oolong tea, on the sensory and motor skills, ASC DSM-5 [1] symptomology, anxieties and sleep of children with ASC.

1.1 Sensorimotor integration and autism

In addition to unusual and repetitive motor mannerisms, individuals with ASC have long been reported as having general ‘clumsiness’ [18-19]. Motor difficulties in ASC have been repeatedly described in research, with motor skills scores for children with ASC reportedly often falling 1.5 standard deviations below the typical mean [20-21]. Motor difficulties affect around 80-90% of individuals with ASC [2-3;22-25] and are present from early infancy [25-28].

Sensory ‘disturbances’ in ASC have also been continually reported since both Kanner’s [18] and Asperger’s [19] pioneering reports. For example, studies have described high prevalence of atypical sensory responsivity, with up to 95% of individuals with ASC showing sensory responsivity dysfunction [29-30], including a variety of sensory responsivity impairments [31-32] such as; differences in proprioceptive impairment (the sense of one’s own relative position in space) [33], hyper- and hypo-responsivity across tactile [34-35], visual [36], olfactory [37] and auditory domains [33,38-40] and perceptual function [41].

Both atypical movement and sensory responsivity have been implicated in the severity of ASC symptoms, such as impaired skilled motor gesture [42], greater anxiety in the playground [30] and atypical processing of both physical and social pain perhaps leading to insensitivity [43]. Studies have also shown correlations between both coordination difficulties and autism symptomology [44] and sensory disturbance and autism severity [45-49]. However, motor coordination and sensory processing are intrinsically connected [50]. For example, sensory feedback is essential to planning and executing the movement of reaching for an object (such as being aware of your own position both visually and proprioceptively) [3, 50]. Consequently, impaired sensory guidance is likely to affect both the ability to acquire and also adjust a stored motor command [51]. This firmly implies that sensory responsivity and motor coordination should not be treated as distinct separate entities, but as a single working unit in the construct of sensorimotor integration. This theory is supported by a number of studies that demonstrate an association between motor coordination and sensory responsivity in ASC (e.g. see 2, 48, 52-58]. Furthermore, Gowen and Hamilton [3] suggest that atypical sensory input and variability in motor deployment ‘together’ may play a crucial role in ASC, a theory supported by research conducted by Hannant et al. [59], where sensorimotor skills are correlated with autism symptomology.

1.2 Sensorimotor pathology, neurology and endocrinology

There are specific areas of the brain associated with sensorimotor integration. These include: the cerebellum, which is considered to be intrinsic to predicting movement outcomes [60] and is thought to contain pathways that are responsible for linking sensory input to motor output [5-6, 61]; and the basal ganglia, also thought to be involved in multisensory integration in addition to automaticity and motor habit [7-8;62-64]. Both brain regions are involved in GABAergic activity. The cerebellum contains Purkinje cells, which are considered the sole output of all motor coordination in the cerebellar cortex [65], whilst the striatum in the basal ganglia contains medium spiny neurons (MSN), also a GABAergic cell [66]. Yet, 95% of autistic

cerebella examined at autopsy had a significantly decreased number of Purkinje cells, [12-14]. In addition, a decreased volume in the basal ganglia [11], and excess functional connectivity in the striatum, one of the largest components of the basal ganglia and consisting of 95% MSN [66], have been reported in ASC [67].

In addition to these pathological abnormalities of the cerebellum and basal ganglia in ASC, neurological differences are also present. Purkinje and MSN cells release the inhibitory neurotransmitter, GABA, which is key in sensory discrimination [15]. GABA is considered essential to reducing and inhibiting sensory feedback and decreases the firing of neurons, regulating brain excitability [68]. Variations in GABAergic transmission have been associated with sleep disorders [69] and hyper-excitable states such as anxiety and epilepsy [70-71]. GABAergic functioning has also been implicated in tactile reactivity and performance [72-73]. Significant reductions of 63% and 61% respectively in $GABA_A$ receptors and the glutamic acid decarboxylase protein (GAD) (the enzyme responsible for converting glutamate into GABA) have been found in ASC in comparison to controls [74-75]. GABA levels have also been shown to be lower in the auditory and motor cortices of children with ASC [16]. In addition, increased glutamate levels in blood and platelets have been found in ASC subjects, suggesting impaired conversion of glutamate to GABA [74,76]. Moreover, a key candidate gene for ASC is the GABA receptor gene, *GABRB3* [77-78]. Furthermore, a study by Green et al., [79] demonstrated that participants with ASC also showed stronger activation of the amygdala towards sensory stimuli, which is thought to perform a pivotal role in emotion processing and decision-making; GABAergic neurons are also present in the amygdala [17,80]. It is noteworthy that GABA is a neurotransmitter of enteric neurons in the mammalian gastrointestinal tract [81] and $GABA_A$ receptors are influenced greatly by testosterone levels [82], where both gastrointestinal difficulties [83] and exposure to high concentrations of testosterone levels prenatally [84] are associated with ASC. Thus, establishing and maintaining a balance between the inhibitory and excitatory responses in this key neural pathway appears to be intrinsically linked to ASC [85].

Early development theories such as Jean Piaget's developmental stage theory proposed that sensorimotor integration was key to neurotypical development and where a child struggles to coordinate their initial sensory experiences, further stages of development will be impaired [86]. Sensorimotor difficulties with or without ASC have a pervasive and serious impact on the emotional well-being of children and young adults [87], which in turn generates greater mental health risk and psychological distress [88]. Consequently, the understanding of GABA's role in sensorimotor development is of great importance. However, in addition to GABA's influence on this sensorimotor chain of emotional well-being, it would also seem that GABA levels

are directly affected by glucocorticoids, such as cortisol, that modulate neuronal excitability by interacting with GABA synthesis and receptors [89-91]. Cortisol is a steroid hormone produced by the adrenal cortex, it regulates both the carbohydrate metabolism and blood pressure, and is released in response to stress. It also plays a key role in the sleep-wake cycle by facilitating wake. Despite inter-individual variability, intra-individual variability tends to be low: levels decrease throughout the day to reach a nadir at around midnight, then rise steadily before dawn and increase sharply upon awakening, known as the cortisol awakening response (CAR) [92]. However, higher cortisol awakening levels (CAL) have been associated with stronger stress responses, and prior day awakening levels are also reported as having a 'carry-over' affect [93: p7]. Cortisol levels have been found to be atypical in individuals with ASC [94-95] and have been associated with greater sensory responsivity in children with ASC [96]. An association between the cortisol stress response and gastrointestinal symptomology in children with ASC has also been reported [97]. As a result, GABA appears to have at least a dual function in the management of anxieties in ASC, both at a sensorimotor and endocrinology level.

A further role of GABA is in its complex association with melatonin; a neurohormone produced in the pineal gland that plays a key role in regulating the sleep-wake cycle by facilitating sleep. Melatonin levels are undetectable during the day but begin to increase in the dim evening light before sleep, peaking between 03:00 and 04:00 [98]. They show a high level of intra-individual day-to-day consistency [99]. Sleep problems in ASC are common, affecting up to around 83% of children [100-102]. They include difficulties initiating and maintaining sleep, early morning waking, short sleep duration and restless sleep, as well as daytime sleepiness. Children with autism also commonly experience anxiety around falling asleep and display behavioural problems such as stalling and resisting going to bed at an appropriate time [102]. The primary indication for sleep problems is thought to be caused by abnormal melatonin circadian rhythms in individuals with ASC, including a reduction in melatonin secretion in over half of individuals with ASC [103-104], where melatonin concentration is reduced by around half [103]. The reduction in melatonin in ASC correlates highly with characteristic autistic behaviours, and treatment with melatonin supplementation improves sleep duration, sleep onset latency, and night time awakenings, as well as daytime behaviour [105]. Rat models suggest that melatonin is mediated by the GABAergic system. Importantly, the location of the endogenous circadian clock which controls the release of melatonin is in the suprachiasmatic nucleus of the hypothalamus (SCN); an area where almost all neurons contain GABA. The interaction between melatonin and GABA-driven mechanisms in the SCN appears to play a key part in the regulation of sleep mechanisms

[106-109]. A dysfunction in the GABAergic system in ASC could therefore be responsible for the reduction in melatonin thereby impacting sleep problems in these individuals.

1.3 Gamma-aminobutyric acid (GABA) and the blood brain barrier (BBB)

The aforementioned evidence base for the involvement of GABA in the sensorimotor impairment, anxieties and sleep of ASC would indicate that increasing GABA levels in ASC might help remediate some of these difficulties and perhaps in turn reduce ASC symptomology. However replacing GABA synthetically is not straightforward, as it has long been believed that GABA cannot penetrate the blood brain barrier (BBB) [110-111], a barrier that specifically protects the brain from toxins [112]. More recently this finding has been challenged [113] and the type of GABA, administration and species of experimentation have been explored. Furthermore, the BBB may be compromised in ASC. The GABAergic neural pathway has been shown to be variable in epilepsy and this is thought to be attributable to a possible break down or failure in the BBB [114-115]. Consequently GABA, in the form of Gabapentin, can be therapeutically prescribed for this condition [116]. Higher rates of epilepsy have also been reported in individuals with ASC than the TD population [117-120], with prevalence estimates ranging from 5 to 26% (median 17%) compared with only 1% prevalence in TD. There is a particularly high prevalence rate (up to 60-76%) of epileptiform discharges in the absence of epilepsy being present in ASC [121-122]. Epileptiform discharges are rare in neurotypical children (1-4%) [123] and are described by the International Federation of Societies for Electroencephalography and Clinical Neurophysiology (IFSECN) glossary of terms as being “distinctive waves or complexes, distinguished from background activity, and resembling those recorded in a proportion of human subjects suffering from epileptic disorders without clinical seizure” [124: 538]. With such a high prevalence rate in ASC Lee et al, [122] suggested that this might be a biomarker of cortical dysfunction. As a consequence, the BBB in the region of an epileptic focus is thought to be more permeable to GABA [125]. Accordingly, GABA may be able to pass the BBB in ASC, although this would doubtless vary depending on the permeability of an individual’s BBB to the neurotransmitter.

This study is the first to explore the effect of introducing a non-evasive GABA substitute, in the form of GABA Oolong tea, on cognitive and behavioural outcomes of children with ASC. Oolong tea has high levels of GABA achieved by alternating the leaves between air and a nitrogen rich environment (with no air) during an oxidation phase. Studies have previously shown that GABA tea has sleep promoting properties [126] in addition to noting the anecdotal evidence on GABA supplements of sedative and calming effects.

Specifically, this study will explore the effect of GABA Oolong tea on sensory responsivity, motor coordination, autism symptomology, sleep quality and duration, and cortisol level. With the consideration that GABA Oolong tea may not cross the BBB a different tea will also be trialled in the study, Gyokuro Green tea, which is high in the compound L-Theanine. L-Theanine is an amino acid analogue of L-glutamate and L-glutamine, readily crosses the BBB, and is thought to increase by proxy the GABA levels within the brain [127-127] by exerting an indirect action on $GABA_A$ receptors [129]. GABA and L-Theanine tea are compared to a placebo tea in this double-blind, placebo controlled, repeated measures study. In comparison to placebo, we hypothesise that drinking GABA Oolong tea will increase coordination skills, decrease sensory difficulties, decrease cortisol awakening levels resulting in lowered 'carry-over' cortisol, improve sleep and ultimately decrease autism symptomology on the DSM-5 scale. Drinking L-Theanine tea (Gyokuro Green tea) should also mirror these effects to a lesser degree. However, varying degrees of effectiveness are expected between individuals due to variability in motor skill, hormone levels and BBB permeability.

2. Method

2.1 Participants

Nine children (5 male, 4 female) aged 9y 5m to 13y 9m (mean age 11y 7m) with confirmed ASC took part in the study. They were recruited from local ASC support groups in Warwickshire and Leicestershire, UK. All nine children had a pre-existing diagnosis of ASC from a trained clinician according to DSM-5 criteria. ASC diagnosis was also confirmed by the research team using the Autism Diagnostic Observation Schedule General – 2nd Edition (ADOS-2) [130], administered by a research reliable rater. Participants were recruited based on APA DSM-5 ASC criteria [1] and various levels of cognitive functioning were apparent, representing the variability and diversity of their individual differences. However, strict inclusion criteria were adhered to: diagnosis of ASC, no known co-occurring ADHD, genetic or medical conditions, no current medication, a willingness to drink tea, the ability to wear a watch without tactile sensitivity, younger than 14 (due to a large increase in testosterone levels after this point (Mayo Foundation for Medical Education and Research website, 1995-2017)), and both parent and child commitment to four university visits and precise tea making and drinking requirements. Sample size was determined based on a feasibility study with strict inclusion criteria and sufficient power in case of statistical analyses. Recruitment occurred from September 2016 to April 2017: study duration from September 2015 to September 2017.

2.2 Materials

Participants completed a battery of performance measures and caregivers completed a set of questionnaires about their child's behaviour. Children's sleep quality and duration were monitored using actigraphy, and saliva samples were collected for analysis of cortisol. Due to the small number of participants being involved in a repeated measures study, the authors chose to test a number of variables (subjective, objective and hormonal) in order to ensure that any findings were further substantiated at various levels of observation. Standard measures of intelligence such as the full scale WASI-II [131], which require a spoken response, appear to underestimate the abilities of children with autism [132]. Therefore, in the current study, performance was ascertained using only the non-verbal IQ matrices subset of the WASI-II [130] and receptive language measure (BPVS-III; [133]).

2.2.1 Performance measures

Autism Diagnostic Observation Schedule – 2nd Edition (ADOS-II; [129]). The ADOS-II is a standardised diagnostic instrument for diagnosis of ASC. It was utilised in the present study to independently confirm participants ASC diagnosis and indicate severity of ASC symptoms in order to ensure full and robust measurement of ASC symptomology. It consists of a semi-structured interview that provides a number of social prompts and opportunities to code quality of social and communicative behaviours. It also includes a rating indicating the severity of ASC symptoms, whilst accounting for the person's age and expressive language level. The ADOS-II was validated on 381 individuals aged between 15 months to 40 years with and without disabilities, with a further 1139 children aged between 14 months to 16 years recruited to revise the algorithms. Inter-rater reliability showed over 80% agreement on all modules with a high level of discriminative validity between autism and TD resulting in specificities of 50 to 84 and sensitivities of 91 to 98 [130]. An age dependent criterion score is used to diagnose ASC, where a higher score indicates more severe autism characteristics.

The British Picture Vocabulary Scale III (BPVS-III; [133]). The BPVS-III is a standardised non-reading assessment of receptive language. Each item within the assessment requires the child to identify the correct image out of four pictures provided, which matches a word provided by the researcher. The test covers a range of subjects, including verbs, animals, emotions, toys and attributes. The BPVS-III was normed on 1480 children aged 3-16 years with and without disabilities. Internal reliability is .91 and validity with the Wechsler Intelligence Scale for Children (2005) = .76 [133]. The BPVS-III has a standardised mean score of 100, where <84 is considered below average and >115 is above average.

Wechsler Abbreviated Scale of Intelligence – 2nd Edition (WASI-II; [131]). The WASI-II is a brief standardised measure of verbal and non-verbal intelligence. The matrices subset was used in the current study to measure non-verbal reasoning. The WASI was normed on approximately 2900 individuals aged 6-90 years with and without disabilities. Matrix Internal Reliability is .87-.94 and validity with the Wide Range Intelligence Test (WRIT) is .71 [131]). The WASI-II provides a standard mean score of 100 for TD children, and where a <84 is considered below average and >115 is considered above average.

2.2.2 Parent-Report Questionnaires

Primary Outcome Measure - The Autism Spectrum Ratings Scale (ASRS; [134]). The ASRS (6-18 Years, Parent form) is used to quantify observations of a child that are associated with ASC. The form is composed of 71 questions based on a Likert scale of Never, Rarely, Occasionally, Frequently and Very Frequently, scoring 0-4. Raw scores are converted into T scores, where T scores above 60 are considered to show increased concern, and are classified as low, average, slightly elevated, elevated and very elevated. Scores can be apportioned into social communication, unusual behaviours and self-regulation, each of which can be further divided into treatment scales for peer socialisation, adult socialisation, social and emotional reciprocity, atypical language, stereotypy, behavioural rigidity, sensory sensitivity and attention. An overall score for ASC based on DSM-5 criteria for an ASC can also be attained and raw scores for the DSM-5 criteria were utilised within this study. Such criteria include difficulties with social communication, unusual behaviours and self-regulation. The ASRS was normed on over 7000 children aged 6-18 years with and without disabilities. Internal reliability was .95-.96 based on the DSM-IV, and the test shows good validity, with 90.3% sensitivity and 92.2% specificity on accurately predicting group membership [134].

Secondary Outcome Measure - Sensory Profile (SP; [135]). The SP is a standardised, 125-item, parent report questionnaire for children aged 3-10 years that assesses the frequency of a child's responses to differing sensory modulation, processing and emotional events. The SP consists of three domains: sensory responsivity, which includes auditory, visual, vestibular, tactile, oral and multi-sensory processing; modulation, which includes modulating sensory responsivity with relation to endurance and tone, proprioception, movement affecting activity, emotional responses and visual filtering; behavioural emotional response, which considers the behavioural outcomes of sensory responsivity. Lower scores on the SP indicate greater difficulties in a particular area of sensory responsivity. The SP was normed on 1187 children aged 3-14 years with and without disabilities. Internal reliability includes internal consistency estimates (range = .47-.91) and convergent and discriminant validity was determined by demonstrating high correlations with scores on the school function assessment [135].

2.2.3 Objective measures

Secondary Outcome Measure - The Movement Assessment Battery for Children – 2 (MABC2. [136]): This is a standardised assessment of motor coordination for children aged 3 - 16 years and is a revision of the Test of Motor Impairment (TOMI; [137]). It is comprised of three components: manual dexterity, ball skill and balance. Examples of test content include placing pegs onto a board, throwing a beanbag onto a target and walking heel to toe along a line. The Movement-ABC 2 was normed on 1172 children aged 3-16 years with and without disabilities. Normed scores for TD children yield a mean score of 100, and where a standardised score of <84 is considered below average and >115 is considered above average; however, in the present study raw scores were used in order to analyse findings from each component in greater detail. Internal reliability includes internal consistency estimates (range = .92-1.00) and validity with the 'Draw-a-Man' test = .66 [138].

Secondary Outcome Measure - Actigraphy sleep monitoring. Participants were asked to wear an actiwatch (Actiwatch 2, Philips Respironics) on their non-dominant wrist to measure sleep quality, duration and timing. Actigraphy provides a reliable and valid method for measuring sleep patterns in a natural setting over a prolonged period and is 80% concordant with laboratory-based sleep studies for determining sleep and wake but benefits from minimal disruption to sleep and routine [139]. Due to individual variability across nights, it is recommended that actigraphy be used for at least five and preferably seven nights to reliably score a person's normal sleep patterns; thus children were requested to wear the actiwatch continuously for one week [140]. Parents were requested to keep a sleep diary of their child's bedtime and wake times, which was used to support analysis of actigraphy data.

Actigraphy data were analysed in one-minute epochs using Philips Actiware (Philips Respironics).

Secondary Outcome Measure - Hormonal sampling. Participants were requested to collect saliva samples via passive drool in the afternoon, the evening before bed, and immediately upon waking. Parents were trained in the use of saliva collection devices and were provided with written instructions. It was requested that children avoid ingesting substances that may interfere with analysis (e.g., chocolate, aspirin) on the day; and avoid eating for at least 30 minutes before the saliva collection. They were requested to rinse their mouth ten minutes before the saliva collection, and then to remain seated and avoid moving around too much. Parents froze the samples immediately and returned them at their appointment in a cool bag with two frozen ice packs. Samples were then frozen at -80°C until the day of analysis.

Prior to assaying, all samples were defrosted and centrifuged for 15 minutes @ 1500g. Cortisol (Cat no. 1-3002) levels were measured using expanded range high sensitivity enzyme immunoassay kits (Salimetrics LLC, State College, PA, USA). Melatonin (Cat no. 1-3402) levels were measured using enzyme immunoassay kits. All saliva specimens were assayed in duplicate and absorbance values determined using a UV-Vis spectrophotometer (Epoch 2, Bio Tek Ltd, Winooski, VT, USA). Unknown values were determined by non-linear regression curve fit software (Prism version 4.0, La Jolla, USA).

Tea intervention. Participants were required to drink three different teas. Each was made using the following method: one tea-loaded 47mm tea infuser, 300ml freshly boiled water, 120 seconds of infusion. Participants were advised that they could drink the tea hot or cold, perhaps adding fruit squash or other flavourings if they preferred, keeping this variable the same for each tea throughout the study. Teas were analysed for exact components by Hungkuang University Functional Food Research Laboratory. The three teas were: GABA Oolong (GABA 279mg/100g, L-Theanine 104.48mg/100g); Placebo Jiao Gu Lan (GABA 157mg/100g, L-Theanine 0mg/100g); L-Theanine Gyokuro Green (GABA 156mg/100g, L-Theanine 1340mg/100g). The placebo needed to be a fluid as it was necessary to ensure that cognition was not influenced by differing daily fluid intake [141]. It was also felt that a sweet and visibly similar fluid that was not tea would be ideal. Jiao Gu Lan is not a tea, but a tisane (a herbal tea). An active placebo was chosen as GABA is found in all teas and tisanes due to the picking process and stress on the plant, however in highly concentrated GABA tea, the leaves are left in low or deficient oxygen environments, further increasing the stress and consequently GABA [142]. Thereby the magnitude of difference in the level of GABA between the GABA tea and placebo was deemed acceptable. The teas were respectively labelled A, B and C and the study was double-blinded to eliminate examiner bias and participation expectancy effects. Teas were given in three orders to counterbalance and combat order affects and ensure an allocation ratio of 1:1. (Participants 1, 2 & 3 received Tea A, B then C; Participants 4, 5 & 6 received Tea B, C then A; Participants 7, 8 and 9 received Tea C, A then B). Order of tea was assigned to next participant thus ensuring a random allocation. The child was requested to drink four 300ml cups of the given tea each day for two weeks. This dosage was calculated based on the necessity to achieve a ‘natural’, non-invasive and safe dose. Readily available GABA supplements varied between doses of 200-750mg. With the GABA Oolong tea the dose would be approximately 280mg per 100g tea. Based on using 3.5g per tea portion this equates to 9.8mg of GABA; multiplied by 4 throughout the day being 39.2mg of GABA. This dose is calculated as almost double the placebo (22.2mg per day of GABA).

2.3 Procedure

Ethical approval for the study was obtained from the Research Ethics Committee. Clinical Trial Registration occurred post-study following study publication guidelines. The authors confirm that all ongoing and related trials for this intervention will be registered. After parental consent to take part in the study was obtained, the parent and child were invited to an assessment session at the University. During this session trained researchers carried out the following assessments: ADOS-II, BPVS III and WASI-II non-verbal subsets. Following this the parent was given the first tea, saliva collection devices and tubes, an actiwatch, sleep diary, and full written instructions. Following seven days of tea, the child wore an actiwatch for seven days. At the end of the second week of drinking the given tea, the parent collected and froze the saliva samples from their child. Parents and children then returned to the University with their saliva samples, actiwatch and sleep diary. The participant's parent completed the SP and ASRS based on their child's behaviour during the previous 2 weeks alone, whilst the child completed the MABC2 with the examiner. They were then provided with the next tea, saliva collection devices and tubes, another actiwatch, sleep diary, and written instructions. This process was followed by a washout week before starting again with the second and third teas. Thus, the process lasted eight weeks. At the end of the eighth week the parent was also asked to write down which tea they felt was most beneficial and which tea was not. This was not shown to the examiner and was sealed in a folder until the end of the study. Table 1 shows the study timetable.

Table 1. *Study Timetable*

WEEK	Activity
1	ADOS-II, BPVS-III, WASI-II (Matrices), Tea 1 start
2	Continue Tea 1, wear actiwatch, on last day take afternoon, evening and next morning saliva samples (freeze)
University visit	Collect saliva samples and actiwatch, parent fill in ASRS and SP based on last two weeks' behaviours, child completes MABC2. Given Tea 2
3	Washout week
4	Start Tea 2
5	Continue Tea 2, wear actiwatch, on last day take afternoon, evening and next morning saliva samples (freeze)
University visit	Collect saliva samples and actiwatch, parent fill in ASRS and SP based on last two weeks' behaviours, child completes Movement ABC. Given Tea 3
6	Washout week
7	Start Tea 3
8	Continue Tea 3, wear actiwatch, on last day take afternoon, evening and next morning saliva samples (freeze)
University visit	Collect saliva samples and actiwatch, parent fill in ASRS and SP based on last two weeks' behaviours, child completes Movement ABC. Parent writes down subjective view of teas.

2.4 Analysis

Data were analysed both qualitatively and quantitatively. Qualitatively parental report of the best and worst tea was utilised. Quantitatively each child's manual dexterity (MABC2), gross motor skills (MABC2), SP, DSM-5 scale, sleep quality and duration, and cortisol levels were analysed separately for differences between the placebo and both GABA tea and L-Theanine Tea, using % difference in proportion to placebo. This analysis was chosen in order to explore the impact of the three tea conditions on a case by case basis, due to the individualism of each participant in addition to the fully holistic approach. Following this, group data were analysed using SPSS (version 24) using a repeated measures ANOVA with a simple contrast to compare scores on each of the above variables for the GABA and L-theanine teas to scores for the placebo tea. The Bonferroni correction was used to correct for multiple comparisons. Cook's distance was used to identify outliers and partial eta squared (ηp^2) noted for Power analysis, where an effect size of above 0.14 was considered large [141]. Where sphericity was violated, the Greenhouse-Geisser estimate was used to adjust degrees of freedom and the *F* statistic, and multivariate statistics with Wilks' Lambda are reported. A nonparametric one sample test was then utilised to query the significance of the parental perceived benefits of the best tea. It is important to note here that participant 9 experienced a period of increased stress during the GABA tea trial.

3. Results

3.1 Background measures

The average age of participants was 11.58±0.58 years (range: 9.42-13.75). The average non-verbal reasoning standardised score was 100.11±4.53 with verbal reasoning at 97.56±6.5. No participant fell below a standardised score of 70 on either the WASI-II (range: 78-125) [131] or the BPVS III (range: 70-121) [133]. The average score on the ADOS-II was 14.67±4.24 (range: 10-21); no participant fell below the cut-off for Autism, thus confirming ASC diagnosis for all children**.**

3.2 Sensory and Motor Measures

Table 2 shows the percentage differences between GABA and the placebo tea for manual dexterity (MABC2), balance (MABC2) and sensory responsivity (SP) for each child. Results show that seven of the nine participants had an improvement in manual dexterity, in that the time it took in seconds to complete the

manual dexterity tasks with more accuracy was decreased compared with the placebo. Five of the nine participants had improved balance as they were able to balance for longer periods of time when compared with the placebo, and six of the nine participants had improved SP total scores indicating as much as 28% reduction in sensory responsivity.

Table 2.

Manual Dexterity, Balance and Sensory Profile with GABA tea Individual Analysis

	Manual Dexterity			Balance			Sensory Profile		
Ppt	Placebo	GABA	% Difference	Placebo	GABA	% Difference	Placebo	GABA	% Difference
1	74.5	75.5	-1.3	34.0	28.0	-17.7	228.0	245.0	**7.5**
2	78.0	71.0	**9.0**	45.0	43.0	-4.4	254.0	309.0	**21.7**
3	82.5	83.5	-1.2	16.5	17.0	**3.0**	280.0	240.0	-14.3
4	48.0	45.0	**6.3**	46.5	44.0	-5.4	247.0	272.0	**10.1**
5	58.0	47.0	**19.0**	39.0	40.0	**2.6**	199.0	254.0	**27.6**
6	101.0	80.5	**20.3**	22.0	34.0	**54.6**	216.0	233.0	**7.9**
7	128.5	94.0	**26.9**	32.0	47.0	**46.9**	283.0	282.0	-0.4
8	81.0	58.5	**27.8**	23.0	24.0	**4.4**	207.0	245.0	**18.4**
9	72.5	70.5	**2.8**	50.0	19.0	-62.0	302.0	214.0	-29.1

Note: Figures in bold indicate improved results when GABA tea is compared to the placebo

Table 3 shows the percentage differences between L-Theanine tea from the placebo tea for manual dexterity (MABC2), balance (MABC2) and sensory responsivity (SP) for each child. Results show that five out of nine had improved manual dexterity with L-Theanine, seven out of nine had improved balance, and six out of nine had improved sensory responsivity.

Data analysis, using a repeated-measures ANOVA to compare the three tea conditions, demonstrated that manual dexterity was significantly different within-subjects, ($F(2, 16) = 3.783$, $p = .045$, $\eta^2 = .321$). Post-hoc contrasts using the Bonferroni correction revealed that manual dexterity increased significantly in the GABA tea condition with large effect ($F(1, 8) = 6.22$, $p = .037$, $\eta^2 = .437$), Repeated measures ANOVA showed no significant difference in scores between the tea conditions in sensory responsivity or balance.

Table 3.

Manual Dexterity, Balance and Sensory Profile with L-Theanine tea Individual Analysis

	Manual Dexterity			Balance			Sensory Profile		
Ppt	Placebo	Theanine	% Difference	Placebo	Theanine	% Difference	Placebo	Theanine	% Difference
1	74.5	79.5	-6.7	34.0	39.5	**16.2**	228.0	216.0	-5.3
2	78.0	84.5	-8.3	45.0	34.0	-24.4	254.0	338.0	**33.1**
3	82.5	75.5	**8.5**	16.5	23.0	**39.4**	280.0	245.0	-12.5
4	48.0	51.0	-6.3	46.5	47.0	**1.1**	247.0	272.0	**10.1**
5	58.0	58.0	0.00	39.0	44.0	**12.8**	199.0	221.0	**11.1**
6	101.0	86.0	**14.9**	22.0	27.0	**22.7**	216.0	222.0	**2.8**
7	128.5	120.5	**6.2**	32.0	35.0	**9.4**	283.0	292.0	**3.2**
8	81.0	53.5	**34.0**	23.0	30.0	**30.4**	207.0	216.0	**4.4**
9	72.5	69.0	**4.9**	50.0	50.0	0.0	302.0	269.0	-11.0

Note: Figures in bold indicate improved results when L-Theanine tea is compared to the placebo

The ball skills composite of the MABC2 demonstrated a limited effect as raw scores improved on average by <1 with aiming and catching and so was not reported.

3.3 Cortisol and Sleep

Table 4 shows the percentage differences between GABA tea from the placebo for sleep, cortisol 'carry-over' effect (the difference between evening and morning cortisol) and cortisol awakening levels (CAL). We investigated several actigraphy indicators of sleep quality and duration: actual sleep time (minutes spent asleep), sleep efficiency (the percentage of time in bed spent asleep), percentage sleep (the percentage time from sleep onset to offset spent asleep), fragmentation (an indicator of restlessness), number of night wakings, minutes of wake after sleep onset, and sleep onset latency. Individual analysis showed no notable differences across the tea conditions, the example included in the table is for mean actual sleep time.

Smaller differences in the cortisol 'carry-over' effect and smaller values in CAL were considered as an indicator of decreased stress. Individual analysis visibly showed that seven of the nine participants had decreased 'carry-over' cortisol levels and decreased CAL with GABA tea; however, repeated measures ANOVAs showed that these effects were not significant.

Table 4:

Mean Actual Sleep Time (minutes), Cortisol 'Carry-Over' effect and CAL individual analysis with GABA tea

	Sleep			Cortisol 'Carry Over' Effect			Cortisol Awakening Levels		
Ppt	Placebo	GABA	% Difference	Placebo	GABA	% Difference	Placebo	GABA	% Difference
1	522.5	529.9	**1.4**	-7.1	-6.5	**6.9**	7.8	8.3	-5.8
2	398.3	391.6	-1.7	10.00	-8.8	**11.5**	10.8	10.4	**4.0**
3	566.7	581.4	**2.6**	-8.5	-7.2	**16.2**	10.4	9.2	**12.0**
4	502.4	503.3	**0.2**	-7.7	-5.5	**28.6**	8.5	7.6	**11.0**
5	452.7	431.3	-4.7	9.0	-9.3	**6.3**	10.9	10.5	**3.4**
6	495.1	465.6	6.0	-3.4	-3.5	-5.6	7.4	4.6	**38.1**
7	410.6	363.9	-11.4	-25.1	-21.0	**16.3**	26.4	22.8	**13.8**
8	479.9	480.2	**0.1**	-8.9	6.0	**33.1**	9.6	6.4	**33.3**
9	496.2	508.3	**2.5**	-9.6	-12.0	-25.1	10.8	13.1	-21.3

Note: Figures in bold indicate improved results when GABA tea is compared to the placebo

Table 5 shows the percentage differences between L-Theanine tea from the placebo for sleep, cortisol 'carry-over' effect (the difference between evening and morning cortisol) and cortisol awakening levels (CAL). Results show no notable difference for mean sleep time, with five out of nine having decreased 'carry-over' cortisol levels, and four out of nine having decreased CAL with L-Theanine.

Table 5:

Mean Actual Sleep Time (minutes), Cortisol 'Carry-Over' effect and CAL individual analysis with L-Theanine tea

	Sleep			Cortisol 'Carry Over' Effect			Cortisol Awakening Levels		
Ppt	Placebo	Theanine	% Difference	Placebo	Theanine	% Difference	Placebo	Theanine	% Difference
1	522.5	543.3	**4.0**	-7.1	-7.8	-9.2	7.8	8.5	-9.8
2	398.3	347.5	-12.8	10.0	-10.4	-4.1	10.8	11.7	-8.4
3	566.7	574.1	**1.3**	-8.5	-5.5	**35.4**	10.4	7.3	**30.2**
4	502.4	454.9	-9.5	-7.7	-7.4	**4.8**	8.5	8.6	-0.8
5	452.7	451.0	-0.4	-9.0	-11.4	-27.8	10.9	12.3	-13.0
6	495.1	466.1	-5.9	-3.4	-0.6	**83.4**	7.4	1.6	**77.9**
7	410.6	402.8	-1.9	-25.1	-6.2	**75.3**	26.4	7.4	**72.0**
8	479.9	433.1	-9.7	-8.9	-10.7	-20.6	9.6	11.6	-20.5
9	496.2	496.3	**0.0**	-9.6	-6.7	**29.9**	10.8	8.8	**18.5**

Note: Figures in bold indicate improved results when L-Theanine tea is compared to the placebo

3.4 DSM-5 Classification (acquired from ASRS)

Table 6 shows the percentage differences between GABA and L-Theanine tea from the placebo tea for the DSM-5 ASC scale; taken from the Autism Ratings Spectrum Scale (ASRS: 134). Results show that five of the nine participants had improved symptoms relating to DSM-5 ASC criteria with GABA tea, and five out of nine with L-Theanine, in that individual DSM-5 scores were decreased. In some cases, individuals showed

as much as a 45% decrease in autism symptomology, meaning that the severity of classification of their ASC was also decreased.

Table 6

DSM-5 Score Individual Analysis

Participant	Placebo	GABA	% Decrease	Classification	L-Theanine	% Decrease	Classification
1	87	85	**2.3**	**Very Elevated to borderline Very Elevated**	84	**3.5**	**Very Elevated to Elevated**
2	88	48	**45.5**	**Very Elevated to Slightly Elevated**	50	**43.2**	**Very Elevated to Slightly Elevated**
3	66	75	-13.6	Slightly Elevated to Elevated	75	-13.6	Slightly Elevated to Elevated
4	75	64	**14.7**	**Elevated to Slightly Elevated**	65	**13.3**	**Elevated to Slightly Elevated**
5	95	57	**40.0**	**Very Elevated to Average**	64	**32.6**	**Very Elevated to Elevated**
6	87	99	-13.8	Very Elevated to Very Elevated	80	**8.1**	Very Elevated to Very Elevated
7	69	78	-13.0	Elevated to Very Elevated	74	-7.3	Elevated to Elevated
8	92	83	**9.8**	**Very Elevated to Elevated**	94	-2.2	Very Elevated to Very Elevated
9	91	128	-40.7	Very Elevated to Very Elevated	98	-7.7	Very Elevated to Very Elevated

Note: Figures in bold had reduced symptoms on the DSM-5 Autism Spectrum criteria with treatment

3.5 Combined Analysis

Figure 1 and Figure 2 show visually the percentage differences between GABA tea and L-Theanine tea from the placebo tea on each variable, where a positive score indicates improved performance.

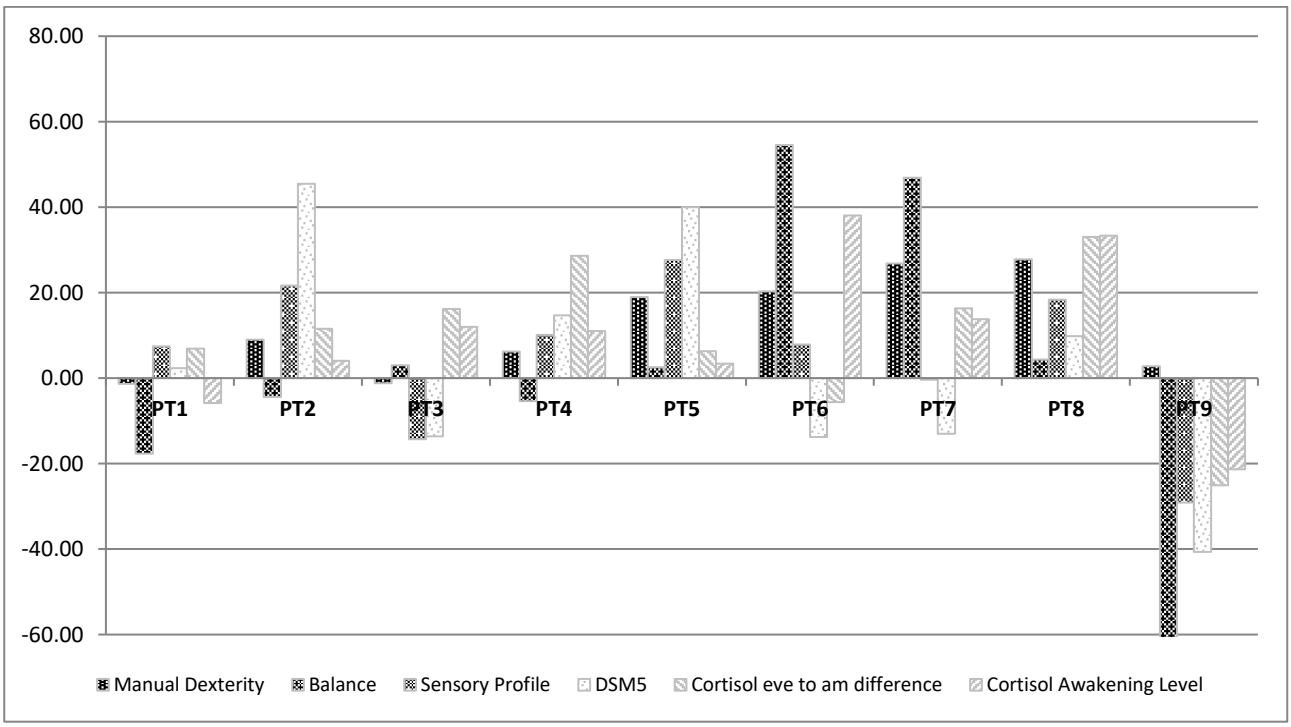

Fig 1. Percentage Difference of GABA Effect from Placebo

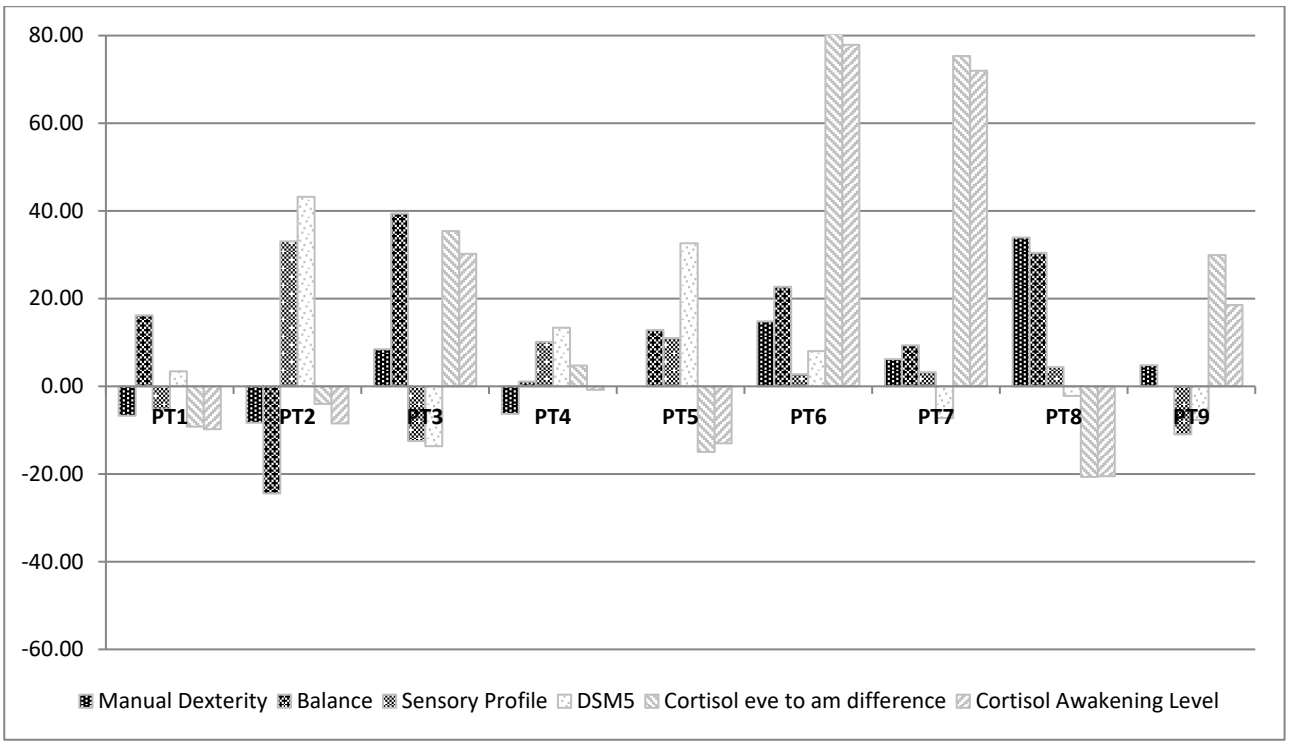

Fig 2. Percentage Difference of L-Theanine Effect from Placebo

Qualitatively, seven out of the nine parents' subjective experience and feedback corroborated that the GABA Oolong tea was the 'best tea', to the point that two parents independently requested more tea and stated that their child 'appeared to sleep more deeply'. When analysing this using a nonparametric one sample test, the perception of best tea was found to be significant (p = 0.018*),* suggesting a rejection of the null hypothesis that GABA as 'best tea' occurred with equal probabilities to the placebo and L-Theanine tea. Moreover, eight out of the nine parents indicated that the placebo was in fact the 'worst tea'. At the end of the study, researchers were able to correctly identify which tea was GABA, L-Theanine and the placebo based on children's patterns of results.

Overall, seven of the nine participants benefited from GABA tea, five appearing to have substantial improvements in sensory and motor control with a large reduction in autism symptomology, with seven participants also having a decrease in CAL and 'carry-over' cortisol levels. Additionally, six of the nine participants benefited from L-Theanine tea, although benefits appeared more sporadic with only three showing improvements in both sensory and motor control.

Only one participant (9) did not appear to be a responder to either tea. This participant experienced high levels of situational anxiety during the GABA tea period and can be easily identified on figure 1. Interestingly, the parent's subjective view of best tea for participant 9 was in fact the L-Theanine tea, noting the placebo as no change from normal.

4. Discussion

The current feasibility study investigated whether a non-invasive GABA substitute, in the form of GABA Oolong tea, affected sensory responsivity, motor coordination, autism symptomology, sleep and cortisol level in children with ASC. Results showed that GABA Oolong tea improved manual dexterity in children with ASC whilst balance improved in over half of the participants. It could be argued that this improvement was a result of practice effects and exposure to task. However, the order of tea conditions was counterbalanced, and this effect was not noted in the L-Theanine condition, or in the Placebo condition, as the participants did not show significant improvements on the task in these tea conditions. Moreover, Bonferroni correction was applied for multiple comparisons. Results also demonstrated that sensory responsivity improved in two-thirds of the participants and autism symptomology decreased in over half, with four of these individuals being positively re-classified on the DSM-5 scale. Differences between evening and morning cortisol levels, deemed the 'carry-over' effect and cortisol awakening levels were also decreased in over two thirds of the participants, which we attribute to a reduction in stress response which may have helped to reduce sensorimotor responsivity in individuals with ASC [96].

Contrary to our hypotheses, GABA Oolong tea did not appear to impact sleep, with no discernible differences noted in a range of sleep parameters compared with the placebo, despite parents' subjective reports that their children appeared to sleep more deeply.

Results also showed that L-Theanine tea also had beneficial results with over two thirds of children having increased balance, two thirds having improved sensory responsivity and over half showing improvements in manual dexterity and autism symptomology. However, with this tea only three participants showed improvement in both sensory and motor control and five children showed a reduction in carry-over and awakening cortisol levels, some with a large increase compared to the placebo.

Our research highlights the importance of examining individual differences in ASC, as considerable between-subjects variability was observed and for this reason we chose to report individual data. Some individuals appeared to benefit greatly from the administration of GABA and L-Theanine tea, some showed a more conservative improvement, whilst a minority actually deteriorated in performance. These differences could be a result of irregularities in the aforementioned situational stress, BBB, coordination abilities and hormone levels of individual children. Future research should investigate the precise factors that could be

used to predict whether an individual will benefit from drinking GABA and/or L-Theanine tea. This would pave the way for data-driven, targeted interventions specifically tailored to the individual.

Combining the mounting evidence for sensorimotor difficulties in ASC, research implies that impaired sensorimotor function in ASC is prevalent, present from an early age and is associated with ASC symptom severity [3,59]. Therefore, with significant impact on manual dexterity and clear gains in balance, sensory responsivity and stress-related cortisol levels after two weeks of drinking tea, in this repeated measures study, the early introduction of children with ASC to GABA Oolong tea could not only decrease anxiety, but also support the sensorimotor development of these children, and perhaps, in turn, reduce autism symptomology. The plausibility of such professedly rapid impact is likely associated with establishing and maintaining a more effective balance between the inhibitory and excitatory responses in key neural pathways [85]. Our data provide initial evidence that GABA and L-Theanine tea could be an effective therapy for some individuals with ASC; thus, the potential for GABA tea in ASC management warrants further investigation. As this was a feasibility study, further research should increase the number of participants taking part, whilst also including children who did not meet criteria for this study, such as those on medication, with co-occurring conditions and within the younger and older stages of childhood, in addition to adults. Moreover, neurodevelopmental conditions that present with motor and sensory difficulties, such as sensory processing disorders or developmental coordination disorder, could also be included in order to support cross-syndrome findings. It is, in these instances, important to consider any possible interactions with medications such as methylphenidate for Attention Deficit Hyperactivity Disorder. The study should also be longitudinal, in order to ascertain any long term changes, and whether any benefits are sustained and/or increased over time. The amount of GABA within the tea could also be a dependent variable; starting at a baseline of zero. This is particularly relevant as the placebo in this feasibility study was active, meaning that the proportion of GABA within the tea is pertinent.

It is important to note that the GABA Oolong tea had 78% more GABA present (GABA 279mg/100g) than the placebo (GABA 157mg/100g), whilst the L-Theanine tea had 1340% more L-Theanine (Theanine 1340mg/100g) than the placebo (Theanine 0mg/100g). Hence, the effect of the GABA tea was substantially greater than the L-Theanine tea when taking tea equivalence into account. However, due to the presence of GABA in the active placebo, this may well have limited the interpretability of the overall effect and for future research a visibly similar fluid excluding GABA would likely be a more effective placebo when measuring potential differences in functioning.

The number of participants that took part in this study was a limitation caused by difficulties in recruiting due to our strict inclusion criteria to minimise extraneous variables. However, this was a very robust feasibility study in that it was repeated-measures with strict participation criteria, and measured a range of variables using a variety of different methods, including parental report, objective sleep monitoring, examiner observation and hormonal assaying. A between groups study of 27 participants would have been equivalent, but would not have had the same insight as treating the same individuals with different teas. A further limitation was that some of the outcomes relied heavily on subjective data from parents. Discrepancies in subjective data can be seen where teas appear to have no influence in the data, however parent report of best tea is contradictory. This would suggest that either overall the parent was able to see a difference in the behaviours of their child but the questionnaires were unable to capture this difference, or the parent thought there was a difference that was not there. Finally, a study such as this cannot account for the turbulent tribulations of life and the impact of this over a short amount of time, which was, in fact, reflected in data from one participant in this study.

In summary, these results provide the first insight to suggest that the sensorimotor abilities, anxiety levels and DSM-5 symptomology of children with ASC can benefit from the administration of GABA in the form of Oolong tea. With the sensorimotor phase of development being a crucial step in successful social and cognitive exploration, further investigation into this neurotransmitter appears to be central to our understanding of ASC. Successful management of ASC through a non-invasive, natural supplement should be welcomed by the ASC community as it may improve life chances and quality of life for individuals with ASC and their families.

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Local Support groups and Parents

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Data Availability Statement:

The data that support the findings of this study are available on request from the corresponding author, PH. The data are not publicly available due to restrictions as their containing information could compromise the privacy of research participants.

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