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GABAergic activity in autism spectrum disorders: An investigation of cortical inhibition via transcranial magnetic stimulation

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ABSTRACT

Mounting evidence suggests a possible role for γ-aminobutyric acid (GABA) in the neuropathophysiology of autism spectrum disorders (ASD), but the extent of this impairment is unclear. A non-invasive, *in vivo* measure of GABA involves transcranial magnetic stimulation (TMS) of the primary motor cortex to probe cortical inhibition. Individuals diagnosed with ASD (high-functioning autism or Asperger's disorder) ($n = 36$ [28 male]; mean age: 26.00 years) and a group of healthy individuals ($n = 34$ [23 male]; mean age: 26.21 years) (matched for age, gender, and cognitive function) were administered motor cortical TMS paradigms putatively measuring activity at $GABA_A$ and $GABA_B$ receptors (i.e., short and long interval paired pulse TMS, cortical silent period). All cortical inhibition paradigms yielded no difference between ASD and control groups. There was, however, evidence for short interval cortical inhibition (SICI) deficits among those ASD participants who had experienced early language delay, suggesting that GABA may be implicated in an ASD subtype. The current findings do not support a broad role for GABA in the neuropathophysiology of ASD, but provide further indication that $GABA_A$ could be involved in ASD where there is a delay in language acquisition.

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1. Introduction

Autism spectrum disorders (ASD) are neurodevelopmental conditions that involve primary deficits in social relating, communication, and behaviour (i.e., repetitive behaviours, restricted interests) and a host of associated features (e.g., sensorimotor abnormalities, abnormal cognitive profile) (Abrahamson et al., 2010). Although the relatively high prevalence of ASD ensures that it is a significant public health issue, the neurobiological basis of these conditions remains largely unknown. Recent evidence suggests a role for the inhibitory neurotransmitter γ-aminobutyric acid (GABA) in the neuropathophysiology of ASD (e.g., Fatemi et al., 2009a, 2009b; Harada et al., 2011). Indeed, a suppression of GABA as underlying autism was suggested a decade ago (Hussman, 2001).

There have been relatively few investigations of the role of GABA in ASD. Among *in vivo* studies, magnetic resonance spectroscopy (MRS) has revealed both reduced GABA and a reduced GABA-to-glutamate ratio in the frontal lobe among 12 children with ASD; thus, ASD may not only involve reduced GABA activity, but pathological increases in glutamatergic function (glutamate is converted to GABA via glutamic acid decarboxylase [GAD]) (Harada et al., 2011). Recent electroencephalography (EEG) research into ASD has also been interpreted as supporting GABAergic deficits among thalamo-cortical networks (Thatcher et al., 2009). Small post-mortem studies among adults with autism ($n = 5–10$) have revealed evidence for $GABA_A$ receptor abnormalities (e.g., reduced receptor density, reduced benzodiazepine binding sites) in the anterior cingulate cortex (ACC) (Oblak et al., 2009), hippocampus (Guptill et al., 2007), prefrontal cortex, parietal cortex, and cerebellum (Fatemi et al., 2009b). Genetic links, such as those related to migration of GABAergic interneurons, have also been suggested (Grigorenko, 2009; Vincent et al., 2006). More recently, there is emerging evidence for $GABA_B$ receptor impairments (Fatemi et al., 2009a, 2010) and cerebellar reductions in GAD (Yip et al., 2009) in autism. (See Aitken, 2008 for a review.)

Transcranial magnetic stimulation (TMS) has been widely used as a non-invasive *in vivo* measure of GABAergic activity (e.g., Berardelli et al., 2008; Croarkin et al., 2011; Daskalakis et al., 2002;

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Fitzgerald et al., 2003, 2008; Gilbert et al., 2005; Levinson et al., 2010; Moll et al., 2000; Ziemann, 2003). A TMS pulse delivered to the primary motor cortex produces a response in peripheral muscle that can be measured via electromyography (EMG). With respect to cortical inhibition, specific paradigms include paired-pulse TMS (ppTMS) and cortical silent period (CSP). ppTMS involves presenting a 'conditioning' pulse prior to a 'test' pulse. Where a subthreshold conditioning pulse is presented a short period before the test pulse (e.g., 2–5 ms; short interval ppTMS), there is typically a suppressed muscle response to TMS, and pharmacological evidence indicates that this reflects activity at $GABA_A$ receptors (e.g., Ziemann et al., 1996). Where a suprathreshold conditioning pulse is presented a somewhat longer period before the test pulse (e.g., 100 ms; long interval ppTMS), there is again a suppressed muscle response to the test pulse, but here pharmacological evidence points to the involvement of $GABA_B$ receptors (McDonnell et al., 2006). By contrast, CSP involves the administration of a TMS pulse during a period of tonic muscle activity, after which there is typically a period of suppressed muscle activity (i.e., the 'silent period'). CSP generally appears to reflect $GABA_B$ activity (e.g., Siebner et al., 1998; Werhahn et al., 1999). It should be noted, however, that CSP has been suggested to reflect either $GABA_A$ or $GABA_B$ receptor activity depending on the stimulus intensity used (Kimiskidis et al., 2006), and some studies have failed to show modulation of CSP via a $GABA_B$ receptor agonist (Inghilleri et al., 1996; McDonnell et al., 2006; Ziemann et al., 1996).

These TMS paradigms have been used with success in elucidating the neuropathophysiology of psychiatric conditions such as depression (Levinson et al., 2010) and schizophrenia (Farzan et al., 2010; Fitzgerald et al., 2003), but to our knowledge have only been employed twice in ASD. Our preliminary study of cortical inhibition in ASD revealed evidence for reduced GABAergic activity in those diagnosed with DSM-IV autistic disorder, but this impairment did not extend to those diagnosed with DSM-IV Asperger's disorder (Enticott et al., 2010). ASD is generally considered a heterogeneous group of conditions, at least from a neurobiological perspective, and it may be that GABA is implicated only in specific autism subtypes, such as those with autistic disorder, who unlike those with Asperger's disorder experience significant early language delay. In the other study, Theoret et al. (2005, see that paper's supplementary material) also examined cortical inhibition via TMS among a small sample of 10 individuals with ASD, but did not discover any significant impairments. They did, however, find a trend toward a reduced CSP in ASD ($p = .07$). Although CSP was not assessed by Enticott et al. (2010), this is suggestive of a reduction in GABA activity in ASD.

Much of the research examining GABA among individuals with ASD has been characterised by relatively small sample sizes, and the precise role that GABA impairments might play in autism and related disorders therefore remains speculative. It is particularly important to explore GABA in ASD because pharmaceutical organisations are currently conducting Phase II clinical trials using GABA agonists in autism. Building upon our previous study (in which we examined only 2 ms and 15 ms ppTMS among a small sample of young individuals with ASD), we aimed to conduct a more comprehensive investigation of cortical inhibition in ASD, including a much larger sample and a broader range of TMS paradigms.

It was hypothesised that individuals with ASD would demonstrate impairments in cortical inhibition reflecting activity at both $GABA_A$ and $GABA_B$ receptors, and that these impairments would be more pronounced for those ASD participants who experienced early language delay (i.e., autism as opposed to Asperger's disorder). Given the suggestion of laterality effects in ASD (e.g., Pierce, 2011), we examined (and where appropriate compared) both cerebral hemispheres.

2. Materials and methods

2.1. Participants

Participants were 36 individuals diagnosed with a DSM-IV high-functioning autism spectrum disorder (ASD) (i.e., high-functioning autism or Asperger's disorder) and 34 healthy controls (i.e., neurotypical [NT]) with cognitive ability assessed to be in the normal range (IQ > 70). Group demographics are presented in Table 1.

ASD participants were recruited via the Monash Alfred Psychiatry Research Centre (MAPrc) participant database, which is comprised of individuals who have previously taken part in research and have agreed to be contacted in relation to future projects, and advertisements placed in newsletters, websites, and offices of ASD-related organisations (e.g., advocacy groups, support groups) and clinicians (e.g., psychologists, psychiatrists, paediatricians). A diagnosis of DSM-IV autistic disorder or Asperger's disorder was confirmed via diagnostic report or with the diagnosing clinician (psychologist, psychiatrist, or paediatrician).

NT participants were recruited via advertisements placed on noticeboards within the Alfred hospital and Monash University. Additional NT child participants were recruited via an advertisement placed within a secondary school newsletter. All participants (or their parents) were asked whether they had ever experienced and/or received treatment for any psychiatric or neurological disorder, including depression and anxiety; any individual that indicated that they had was not included in the study.

Of the 36 ASD participants, 13 were currently taking psychotropic medication. These are presented in Table 2, together with their ASD subgroup (presence or absence of language delay; see Results). None of the NT participants were taking psychotropic medication.

This project was approved by the human research ethics committees of Monash University, Southern Health, and the Alfred hospital. All participants provided signed informed consent to the research and the publication of results. In the case of minors (i.e., <18 years of age), signed informed consent was provided by a parent or legal guardian.

2.2. Procedure

Participants completed a TMS experiment assessing various aspects of cortical inhibition and cortical excitation/facilitation.

2.2.1. Transcranial magnetic stimulation

Single pulse TMS (Magstim-200 stimulator, Magstim Company Ltd, UK) was administered to M1 using a hand-held, 70 mm figure-of-eight coil that was positioned against the scalp using the orthodox method (handle pointing backwards and angled 45° away from midline). Paired pulse TMS (ppTMS) was administered using the same coil and two Magstim-200 stimulators that were linked via a bistim device. Motor-evoked potentials (MEPs) were recorded from the contralateral first dorsal interosseous (FDI) muscle. EMG was recorded using self-adhesive electrodes. EMG was amplified via a PowerLab/4SP system (AD instruments, Colorado Springs, CO),

Table 1
Demographic and clinical characteristics.

	ASD	NT	*p*
N	36	34	
Age (years)	26.00 (10.48)	26.21 (6.60)	n.s. (*t*)
N adolescents (aged 14–19)	11	7	n.s. (χ^2)
N adults (aged 20+)	25	27	n.s. (χ^2)
Gender (m:f)	28:8	23:11	n.s. (χ^2)
Years of formal education	14.56 (4.03)	17.44 (3.65)	.003 (*t*)
Handedness (r:l:a)	27:5:4	30:4:0	
KBIT-2 VIQ	99.94 (17.22)	106.36 (13.18)	n.s. (*t*)
KBIT-2 PIQ	107.25 (19.11)	110.88 (13.10)	n.s. (*t*)
KBIT-2 FSIQ	104.36 (19.34)	110.39 (13.38)	n.s. (*t*)
AQ	30.91 (8.61)	12.32 (5.89)	<.001 (*t*)
RAADS			
Social relating	41.21 (14.86)	14.75 (10.33)	<.001 (*t*)
Language communication	33.18 (13.25)	8.47 (5.46)	<.001 (*t*)
Sensorimotor	31.39 (15.89)	8.19 (6.22)	<.001 (*t*)
Total	105.79 (39.15)	31.41 (18.74)	<.001 (*t*)
DBC total	53.00 (28.46)	1.00 (–)	n.s. (*t*)
DBC autism screen	18.25 (9.62)	1.00 (–)	n.s. (*t*)

Abbreviations: KBIT-2: Kaufman Brief Intelligence Test 2nd Edition; VIQ: Verbal Intelligence Quotient; PIQ: Performance Intelligence Quotient; FSIQ: Full-scale Intelligence Quotient; AQ: Autism spectrum Quotient (Baron-Cohen et al., 2001); RAADS: Ritvo Autism-Aspergers Diagnostic Scale (adult participants only) (Ritvo et al., 2008); DBC: Developmental Behaviour Checklist (child participants only) (Einfeld and Tonge, 2002).

Table 2
Psychotropic medication among 13 ASD participants.

Participant	Early language delay	Medication (dosage per day)
1	Yes	fluoxetine (5 mg)
2	Yes	citalopram (not known)
3	Yes	sertraline (50 mg), lorazepam (2 mg), olanzapine (10 mg)
4	Yes	venlafaxine (150 mg)
5	Yes	fluoxetine (20 mg)
6	No	fluoxetine (40 mg), risperidone (2 mg)
7	No	sertraline (100 mg)
8	Yes	risperidone (2.5 mg)
9	No	mirtazapine (45 mg)
10	Yes	fluoxetine (40 mg)
11	No	sertraline (100 mg)
12	Yes	quetiapine (not known), mirtazapine (not known)
13	No	sertraline (140 mg), risperidone (2 mg), lorazepam (PRN, 1 mg)

and sampled via a CED Micro 1401 mk II analogue-to-digital converting unit (Cambridge Electronic Design, Cambridge, UK).

TMS was firstly used to locate the appropriate site on the primary motor cortex (i.e., M1, the scalp site producing a maximal response in contralateral FDI) and determine resting and active motor thresholds. Consistent with previous TMS research, resting motor threshold (RMT) was defined as the lowest stimulation intensity that produced a peak-to-peak MEP of >50 μV in at least three out of five consecutive trials (e.g., Cirillo et al., 2009). Active motor threshold (AMT) was defined as the lowest stimulation intensity that, during muscle contraction, produced a peak-to-peak MEP of >100 μV in at least one out of five consecutive trials (e.g., Fitzgerald et al., 2009).

Twenty MEPs were then recorded following single pulse TMS (ten at 115% RMT, ten at 130% RMT). There was a four-second interval between each pulse. Immediately after, CSP (Cantello et al., 1992) was determined via 20 single TMS pulses (10 at 115% AMT, 10 at 130% AMT) during voluntary muscle contraction. This was achieved by having participants depress, with their index finger, a set of scales to 400 g, and maintain this during their 20 TMS pulses. ppTMS (Kujirai et al., 1993) was then assessed firstly by administering a randomised block of 45 trials (4s ISI), which included (a) single pulses, (b) paired pulses that were separated by 2 ms (i.e., subthreshold pulse [90% AMT] followed 2 ms later by suprathreshold pulse [120% RMT], thus indexing short-interval cortical inhibition [SICI]), and (c) paired pulses that were separated by 15 ms (i.e., subthreshold pulse [90% AMT] followed 15 ms later by suprathreshold pulse [120% RMT], thus indexing cortical facilitation [CF]), and lastly by a block of 15 trials each involving paired pulses separated by 100 ms (suprathreshold pulse [120% RMT] followed 100 ms after by another suprathreshold pulse [120% RMT], i.e., long-interval cortical inhibition [LICI]).

All of the above measures were completed for both cerebral hemispheres. Specific parameters (e.g., TMS intensity, intervals) were selected based on those that have been used successfully in our lab to examine other clinical populations (e.g., Fitzgerald et al., 2003, 2009).

2.3. Data analysis

MEPs were analysed after determining peak-to-peak amplitudes (achieved via Signal 3.8, Cambridge Electronic Design, Cambridge, UK). Resting trials in which there was evidence of tonic muscle activity within 200 ms prior to the TMS pulse were excluded (<0.5% of all trials). CSP was determined by calculating the time (ms) from the beginning of the MEP to the end of the CSP (i.e., upon resumption of tonic EMG activity) (Daskalakis et al., 2003). Mean values were used throughout. Independent samples *t*-tests were used when comparing ASD and NT groups on most dependent measures (i.e., resting and active motor thresholds, resting and active MEP amplitude following single pulse TMS, CSP). The only exception to this was for 2/15 ms ppTMS, where we conducted a 2 (group: ASD, NT) × 2 (hemisphere) × 3 (TMS condition: single pulse, 2 ms ISI, 15 ms ISI) mixed model ANOVA, and 100 ms ppTMS, where we conducted a 2 (group: ASD, NT) × 2 (hemisphere) × 2 (TMS condition: single pulse, 100 ms ISI) mixed model ANOVA. Independent samples *t*-tests were also used for comparing SICI (i.e., response to 2 ms ISI as a percentage of response to single pulse), CF (i.e., response to 15 ms ISI as a percentage of response to single pulse), and LICI (i.e., response to 100 ms ISI as a percentage of response to single pulse). Data were screened for normality via inspection of boxplots and a formal test of normality (i.e., Kolmogorov–Smirnov [KS]). Where necessary, data transformations (square root or logarithmic) were conducted to ensure normality. Non-normality was detected for resting and active MEP amplitudes (both 115% and 130% RMT) and LICI in both hemispheres, and in this instance a logarithmic transformation provided the most suitable solution (KS $p > .05$). Non-normality was also detected for SICI data (both hemispheres), but here a square root transformation was most suitable (KS $p > .05$).

Given that we have previously found evidence for a dissociation in TMS-indexed GABAergic function based on early language impairment in ASD (Enticott et al., 2010), we further investigated whether there were any differences on these measures between ASD individuals with early language delay (ASD-LD, i.e., no phrase speech before age 3) and ASD without early language delay (ASD-ND, i.e., phrase speech before age 3). This subtyping approach to ASD has been used in past neurobiological research in ASD (e.g., Lotspeich et al., 2004; McAlonan et al., 2009), and has yielded neurobiological differences. Comparisons within the ASD group (i.e., language delay vs. no language delay vs. NT group) were conducted via ANOVA. We lacked the necessary power for mixed-model ANOVA for the ppTMS paradigms, and only conducted ANOVA on SICI, CF, and LICI data.

3. Results

3.1. ASD vs. NT

Summary data, together with *t*-test results where performed, are presented in Table 3.

The ASD group had higher right (but not left) hemisphere resting, $t(64) = 2.39$, $p = .020$, $\eta_p^2 = .071$, and active motor thresholds, $t(62) = 2.23$, $p = .029$, $\eta_p^2 = .062$ (both tests adjusted following unequal variances).

One ASD participant did not complete ppTMS. For the 2 ms/15 ms block, there was an effect of condition (Huynh–Feldt correction, based on $\varepsilon > 0.75$ [Girden, 1992]), $F(1,96) = 142.87$, $p < .001$, $\eta_p^2 = .681$. As expected, ppTMS with a 2 ms ISI produced a significantly reduced MEP compared to single pulse TMS ($p < .001$), while ppTMS with a 15 ms ISI produced a significantly increased MEP compared to single pulse TMS ($p < .001$). This reflects SICI and CF, respectively. There was no main effect of group, $F(1,67) = 0.12$, $p = .733$, $\eta_p^2 = .002$, or hemisphere, $F(1,67) = 0.60$, $p = .440$, $\eta_p^2 = .009$. There was no interaction effect for group × condition (Huynh–Feldt correction, based on $\varepsilon > 0.75$ [Girden, 1992]), $F(1,96) = 0.82$, $p = .407$, $\eta_p^2 = .012$, group × hemisphere, $F(1,67) = 0.17$, $p = .684$, $\eta_p^2 = .002$, or condition × hemisphere (Greenhouse–Geisser correction, based on $\varepsilon < 0.75$ [Girden, 1992]), $F(2,104) = 0.43$, $p = .602$, $\eta_p^2 = .006$. The three way interaction was also not significant (Greenhouse–Geisser correction, based on $\varepsilon < 0.75$ [Girden, 1992]), $F(2,103) = 0.24$, $p = .726$, $\eta_p^2 = .004$. When converted to a percentage of the response to single pulse TMS, there was no effect of group on SICI for either the right, $t(67) = 0.95$, $p = .346$, $\eta_p^2 = .013$, or left hemisphere, $t(65) = 1.30$, $p = .198$, $\eta_p^2 = .025$. Similarly, there was no effect of group on CF for either the right, $t(66) = -1.27$, $p = .210$, $\eta_p^2 = .024$, or left hemisphere, $t(66) = 0.29$, $p = .774$, $\eta_p^2 = .001$.

Three ASD participants did not complete 100 ms ISI ppTMS. For the 100 ms block, there was an effect of condition, $F(1,65) = 187.72$, $p < .001$, $\eta_p^2 = .743$, with a 100 ms ISI producing a significantly reduced pulse when compared with the first pulse in the sequence. This reflects LICI. There was no main effect of group, $F(1,65) = 0.03$, $p = .876$, $\eta_p^2 = .000$, or hemisphere, $F(1,65) = 0.66$, $p = .421$, $\eta_p^2 = .010$. There was no interaction effect for group × condition, $F(1,65) = 0.07$, $p = .789$, $\eta_p^2 = .001$, group × hemisphere, $F(1,65) = 0.49$, $p = .488$, $\eta_p^2 = .007$, condition × hemisphere, $F(1,65) = 1.19$, $p = .279$, $\eta_p^2 = .018$, or group × condition × hemisphere, $F(1,65) = 0.63$, $p = .429$, $\eta_p^2 = .010$. When converted to a percentage of the response to single pulse TMS, there was no effect of LICI for either the right, $t(66) = 0.61$, $p = .546$, $\eta_p^2 = .006$, or left hemisphere, $t(65) = -0.24$, $p = .810$, $\eta_p^2 = .001$.

Several participants were excluded from CSP analyses (3 ASD and 6 NT) due to technical difficulties when recording the data. There were no group differences in CSP for either the right or left hemisphere. Repeated measures ANOVA (TMS intensity × hemisphere × group) also revealed no effect of group × TMS intensity, $F(1,57) = 1.39$, $p = .243$, $\eta_p^2 = .024$, group × hemisphere, $F(1,57) = 0.03$, $p = .856$, $\eta_p^2 = .001$, or

Table 3
Mean TMS outcome measures (untransformed) for ASD and NT groups (SD in parentheses).

	ASD	NT	t	df	p	η_p^2
Resting motor threshold (%)						
Right hemisphere	45.23 (8.00)	41.09 (6.28)	2.39	64	.020	.071
Left hemisphere	45.6 (8.79)	42.88 (6.29)	1.47	67	.145	.027
Active motor threshold (%)						
Right hemisphere	36.31 (6.86)	33.09 (5.04)	2.23	62	.029	.062
Left hemisphere	37.00 (6.33)	34.62 (6.72)	1.53	68	.131	.033
Motor evoked potential amplitude (mV)						
Resting right hemisphere 115% RMT	0.72 (0.90)	0.62 (0.60)	0.19	67	.854	.001
Resting right hemisphere 130% RMT	0.63 (0.46)	0.70 (0.43)	−0.33	67	.746	.002
Resting left hemisphere 115% RMT	0.90 (0.98)	0.85 (1.39)	0.57	67	.574	.005
Resting left hemisphere 130% RMT	1.80 (1.74)	1.86 (2.03)	−0.10	66	.923	.000
Active right hemisphere 115% AMT	0.39 (0.31)	0.49 (0.50)	−0.36	67	.718	.002
Active right hemisphere 130% AMT	2.04 (1.31)	2.79 (2.09)	−0.57	67	.569	.005
Active left hemisphere 115% AMT	1.06 (0.67)	1.26 (1.08)	−0.61	68	.545	.005
Active left hemisphere 130% AMT	2.29 (1.70)	2.77 (2.13)	−0.94	66	.351	.013
ppTMS right hemisphere single pulse	1.02 (1.04)	0.95 (0.69)				
ppTMS right hemisphere 2 ms ISI	0.45 (0.53)	0.42 (0.44)				
ppTMS right hemisphere 15 ms ISI	1.29 (1.22)	1.25 (1.04)				
ppTMS right hemisphere single pulse (−100)	1.01 (1.23)	0.92 (0.77)				
ppTMS right hemisphere 100 ms ISI	0.23 (0.25)	0.18 (0.16)				
ppTMS left hemisphere single pulse	1.11 (1.28)	1.23 (1.36)				
ppTMS left hemisphere 2 ms ISI	0.43 (0.53)	0.54 (0.87)				
ppTMS left hemisphere 15 ms ISI	1.49 (1.77)	1.43 (1.43)				
ppTMS left hemisphere single pulse (−100)	1.14 (1.18)	1.12 (1.23)				
ppTMS left hemisphere 100 ms ISI	0.22 (0.28)	0.27 (0.40)				
Cortical silent period (ms)						
Right hemisphere CSP 115% AMT	57.06 (23.31)	52.10 (15.77)	0.94	57	.352	.015
Right hemisphere CSP 130% AMT	96.42 (39.84)	87.39 (38.36)	0.89	58	.377	.013
Left hemisphere CSP 115% AMT	57.21 (31.18)	54.18 (25.39)	0.41	60	.680	.003
Left hemisphere CSP 130% AMT	92.89 (41.31)	83.11 (36.23)	0.98	60	.331	.016

group × TMS intensity × hemisphere, $F(1,57) = 0.20$, $p = .656$, $\eta_p^2 = .004$.

The above analyses were repeated without those ASD participants who were medicated. The only change was that the difference in active motor threshold for the right hemisphere was no longer significant, $t(55) = 1.47$, $p = .149$, $\eta_p^2 = .038$.

3.2. *ASD subtypes: the impact of early language delay*

There were 16 ASD-LD (12 male; mean age: 25.85 [8.13]) and 20 ASD-ND (15 male; mean age: 24.62 [9.57]). There was no difference in the rates of medicated participants per group (ASD-LD: 8 medicated; ASD-ND: 5 medicated; $\chi^2(1) = 2.41$, $p > .05$). There were no significant differences between these groups in any of the self-report clinical measures of ASD (all $p > .05$), but there was a trend toward a difference in VIQ (ASD-LD: 94.06 [16.68]; ASD-ND: 104.65 [16.56]), $t(34) = -1.90$, $p = .066$.

Summary data, together with ANOVA results where performed and not reported in text, are presented in Table 4, Figs. 1 and 2. We again used the transformed data where appropriate (i.e., logarithmic transformation for resting/active MEP amplitudes and LICI, square root transformation for SICI).

There was an effect of group on RMT in the right hemisphere, $F(2,66) = 3.54$, $p = .035$, $\eta_p^2 = .097$. Post-hoc tests (Bonferroni corrected) revealed an increased resting motor threshold among the ASD-ND group relative to controls ($p = .031$). There were no other between-group differences in motor threshold, and no group effects on MEP amplitude.

For ppTMS, there was an effect of group on SICI for the left hemisphere, $F(2,64) = 4.55$, $p = .014$, $\eta_p^2 = .125$. Post-hoc tests (Bonferroni corrected) revealed that the ASD-LD group had reduced SICI compared with both the ASD-ND ($p = .027$) and NT groups ($p = .027$). By contrast, there was no effect of group on SICI for the right hemisphere, $F(2,66) = 1.60$, $p = .210$, $\eta_p^2 = .046$. There was no effect of group on CF for either the right, $F(2,65) = 0.92$, $p = .405$, $\eta_p^2 = .027$, or left hemisphere, $F(2,65) = 0.55$, $p = .581$, $\eta_p^2 = .017$. There was no effect of group on LICI for either the right, $F(2,65) = 0.21$, $p = .813$, $\eta_p^2 = .006$, or left hemisphere, $F(2,64) = 0.63$, $p = .539$, $\eta_p^2 = .019$ (see Fig. 1).

For CSP, there was an effect of group on right hemisphere CSP (115% AMT), $F(2,57) = 3.26$, $p = .046$, $\eta_p^2 = .103$. Post-hoc comparisons suggested a trend toward an increase in CSP among the ASD-ND group, but comparisons with both the ASD-LD ($p = .079$) and NT groups ($p = .095$) were not significant following Bonferroni correction. There was no effect of group for right hemisphere CSP (130% AMT), $F(2,58) = 1.63$, $p = .205$, $\eta_p^2 = .053$, left hemisphere CSP (115% AMT), $F(2,60) = 0.56$, $p = .574$, $\eta_p^2 = .018$, or left hemisphere CSP (130% AMT), $F(2,60) = 1.58$, $p = .215$, $\eta_p^2 = .050$ (see Fig. 2). As with data comparing ASD and NT groups, repeated measures ANOVA (TMS intensity × hemisphere × group) also revealed no effect of group × TMS intensity, $F(2,56) = 1.02$, $p = .367$, $\eta_p^2 = .035$, group × hemisphere, $F(2,56) = 0.03$, $p = .969$, $\eta_p^2 = .001$, or group × TMS intensity × hemisphere, $F(2,56) = 0.24$, $p = .789$, $\eta_p^2 = .008$.

4. Discussion

The current findings do not support the hypothesis that ASD, as broadly defined, is associated with deficits in cortical inhibition. This is despite an emerging literature suggesting that GABA may be closely involved in the neuropathophysiology of ASD. When considering subtypes, however, there was evidence for some reductions in cortical inhibition, presumably reflecting GABAergic impairments, among those with early language delay (i.e., high-functioning autism); specifically, where there was an early language delay, there was some evidence for a cortical inhibition deficit in the left hemisphere (SICI).

These findings indicate that $GABA_A$ (SICI) deficits may exist in individuals diagnosed with an ASD who have exhibited a delay in language acquisition, but that there may be laterality effects. That

Table 4
Mean TMS outcome measures (untransformed) for ASD-LD and ASD-ND groups (SD in parentheses; NT values included where comparisons performed).

	ASD-LD	ASD-NLD	NT	*F*	df	*p*	η_p^2
Resting motor threshold (%)							
Right hemisphere	43.69 (8.00)	46.53 (7.98)	41.09 (6.28)	3.54	2,66	.035	.097
Left hemisphere	45.88 (8.55)	45.37 (9.21)	42.88 (6.29)	1.09	2,66	.342	.032
Active motor threshold (%)							
Right hemisphere	35.44 (6.56)	37.05 (7.19)	33.09 (5.04)	2.76	2,66	.070	.077
Left hemisphere	37.06 (6.41)	36.95 (6.44)	34.62 (6.72)	1.15	2,67	.323	.033
Motor evoked potential amplitude (mV)							
Resting right hemisphere 115% RMT	0.71 (0.53)	0.75 (1.17)	0.62 (0.60)	0.14	2,66	.869	.004
Resting right hemisphere 130% RMT	0.70 (0.58)	0.57 (0.33)	0.70 (0.43)	0.06	2,66	.940	.002
Resting left hemisphere 115% RMT	1.01 (1.26)	0.81 (0.71)	0.85 (1.39)	0.16	2,66	.855	.005
Resting left hemisphere 130% RMT	2.23 (2.38)	1.38 (0.82)	1.86 (2.03)	0.08	2,65	.924	.002
Active right hemisphere 115% AMT	0.33 (0.23)	0.43 (0.37)	0.49 (0.50)	0.50	2,66	.607	.015
Active right hemisphere 130% AMT	0.80 (0.52)	0.78 (0.42)	2.79 (2.09)	0.18	2,66	.832	.006
Active left hemisphere 115% AMT	1.09 (0.81)	1.06 (0.57)	1.26 (1.08)	0.25	2,67	.780	.007
Active left hemisphere 130% AMT	2.47 (2.19)	2.16 (1.22)	2.77 (2.13)	0.44	2,65	.648	.013
ppTMS right hemisphere single pulse	0.90 (0.68)	1.14 (1.30)					
ppTMS right hemisphere 2 ms ISI	0.55 (0.66)	0.39 (0.38)					
ppTMS right hemisphere 15 ms ISI	1.14 (0.93)	1.41 (1.48)					
ppTMS right hemisphere single pulse (−100)	0.94 (0.65)	1.12 (1.63)					
ppTMS right hemisphere 100 ms ISI	0.23 (0.17)	0.23 (0.32)					
ppTMS left hemisphere single pulse	1.37 (1.75)	0.86 (0.68)					
ppTMS left hemisphere 2 ms ISI	0.60 (0.72)	0.28 (0.24)					
ppTMS left hemisphere 15 ms ISI	1.77 (2.47)	1.17 (0.79)					
ppTMS left hemisphere single pulse (−100)	1.29 (1.51)	0.99 (0.87)					
ppTMS left hemisphere 100 ms ISI	0.30 (0.36)	0.16 (0.16)					

is, evidence of a $GABA_A$ deficit was only found in the left hemisphere. As recently reviewed by Levinson et al. (2010), these inferences are based on numerous pharmacological studies demonstrating that GABAergic agents have a modulating effect on TMS cortical inhibition paradigms; for example, GABAergic agonists seem to enhance SICI (Ziemann et al., 1996). The current results are partly consistent with our previous study, where bilateral $GABA_A$ deficits were found among those with ASD and an early language delay (Enticott et al., 2010). To a degree, this is consistent with the emerging body of evidence concerning the possible role of GABA in ASD, where both $GABA_A$ and $GABA_B$ have been implicated, but again suggests that it is only a specific subtype (i.e., those with early language delay) that are affected, and that any impairments are not particularly extensive. Interestingly, many previous studies that implicate GABA have employed groups of individuals diagnosed with autistic disorder (e.g., Fatemi et al., 2009b; Guptill et al., 2007; Oblak et al., 2009), where in line with diagnostic criteria there were presumably language delays (American Psychiatric Association, 2000).

With respect to the functional significance of GABA, these deficits may simply underpin language impairments in this group. Clinically, there was no significant difference between the two ASD groups on any of the measures used, and a language-based explanation would therefore be the most obvious one. For instance, GABA deficits detected in this sample may have been present from early childhood, and contributed toward impaired language acquisition and development. This would seem particularly relevant to SICI impairments, which were found in the left hemisphere (i.e., crucial to speech production). Alternatively, it is possible that GABAergic impairments in the ASD-LD group relate to repetitive

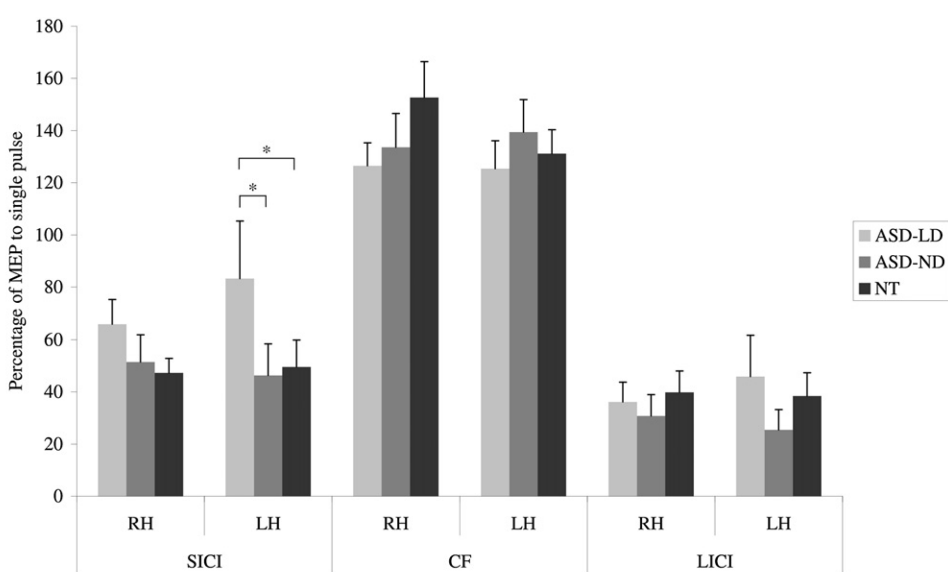

Fig. 1. ppTMS results (absolute mV response to ppTMS expressed as a percentage of absolute mV response to single pulse TMS that was included in each ppTMS protocol) for ASD-LD, ASD-ND, and NT groups.

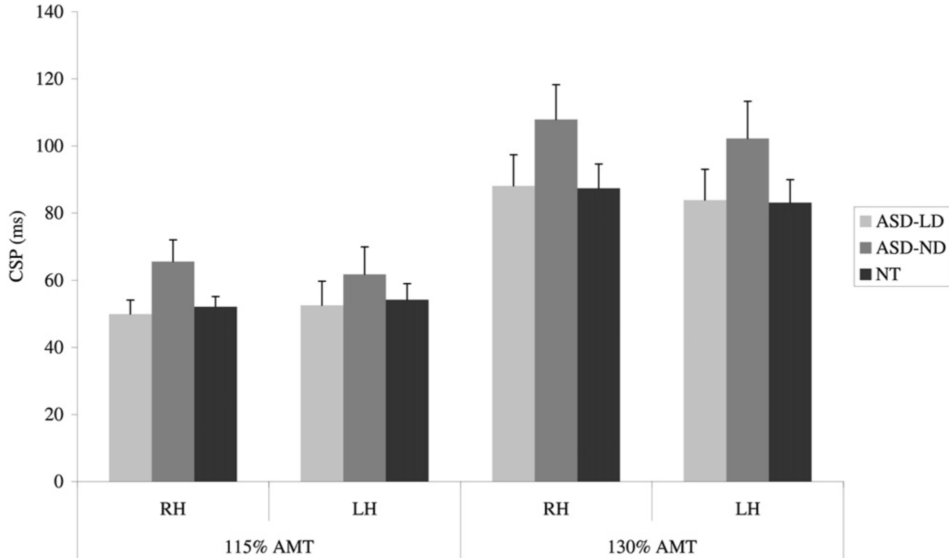

Fig. 2. CSP results for ASD-LD, ASD-ND, and NT groups.

behaviours that form part of the diagnostic criteria (although this would presumably be expected for ASD-ND also), or even broader neurobiological (e.g., neural connectivity) or regulatory processes related to, for example, motor function, social relating, or sensory integration. This would be consistent with, for example, studies of motor function that suggest increased variability among those with high-functioning autism (compared with Asperger's disorder) (Rinehart et al., 2006). That GABAergic deficits were not found in a clinically similar group is consistent with the notion that there are different neurobiological pathways to ASD; that is, different neurobiological impairments might produce characteristically similar clinical presentations, or even have similar effects at a neural level. There is general agreement that ASDs are a highly heterogeneous group of disorders, and this heterogeneity is perhaps the reason that we failed to find any overall between-group effects when comparing ASD and NT groups. While aetiologies remain unclear, there appear to be numerous genetic factors that can be associated with ASD, although at present these only explain 10–20% of individuals with an ASD diagnosis (State, 2010). Thus, it is highly likely that ASDs comprise separate neurobiological profiles that together produce a clinically identifiable syndrome of impairments.

It is interesting that, despite a larger sample, the GABA impairments were seemingly not as widespread as in our earlier study (Enticott et al., 2010), where bilateral deficits were found. The major difference between these studies is that the current sample was older, and that may simply reflect developmental effects whereby the magnitude of these impairments dissipates as people with ASD and early language delay get older.

Interestingly, when comparing the ASD and NT groups, there was some evidence for differences in motor threshold. This refers to the intensity of the magnetic field required to generate a MEP of a predetermined amplitude. This difference was significant only for the right hemisphere. When examining subgroups, this only held for the ASD-ND group (although this analysis was likely underpowered). This finding is inconsistent with Theoret et al. (2005), although this likely reflects the heterogeneity of ASD. While increased motor threshold may be interpreted as an excitatory deficit, or even enhanced inhibition, there are many factors that contribute to one's motor threshold. One such factor is the scalp to cortex distance (McConnell et al., 2001); thus, it might be determined that ASD is overall associated with a greater distance between the scalp and the cortex, and this might relate to altered patterns of brain development (Courchesne et al., 2011). Cortical thinning in ASD might also contribute to this difference (e.g., Hadjikhani et al., 2006). Furthermore, if this finding was indeed related to neurophysiological differences in excitability or inhibition then we would have expected to see this on our other measures (e.g., MEP amplitude), but this was not the case. Interestingly, there have been inverse relationships found between motor threshold and the integrity of white matter pathways in numerous regions (including motor regions and the internal capsule; Kloppel et al., 2008), and there is also evidence of white matter abnormalities in ASD (Stigler et al., 2011); thus, our results might reflect abnormalities in the autistic brain's micro-architecture. These possibilities, however, are highly speculative, and further research that combines brain stimulation and neuro-imaging techniques in ASD will be critical to uncovering the true nature of this relationship.

The current findings are particularly relevant to contemporary autism research and clinical practice. There is an increasing trend toward the study of 'autism spectrum disorders,' which incorporates a host of pervasive developmental disorders, all with impaired social relating at their core, rather than 'splitting' disorders according to DSM-IV-TR nosology (e.g., autistic disorder, Asperger's disorder). It appears likely that DSM-V will not include these separate diagnoses, but instead refer to ASD. This is despite, as indicated, ASD generally being regarded as a highly heterogeneous disorder with multiple underlying aetiologies and pathophysiologies. We are clearly in the initial stages of forging a more complex understanding of the neurobiology of ASD, but an approach that utilises subtypes, be they phenotypical or genotypical, might provide the greatest insights and opportunities for individualised treatment. By contrast, examining broadly defined groups of individuals means that differences between subgroups of individuals, particularly subtle differences, are likely to be missed (as demonstrated in the present study). Without reliable subtyping of ASD, this will arguably further obscure attempts at elucidating the neurobiological basis of these conditions, and thus prevent the development of biomedical treatments. Related to this, these findings are also particularly timely given current clinical trials assessing the use of GABA agonists among individuals with ASD. It is clear that more investigative work is needed to establish the precise nature of GABAergic function in ASD, and to therefore determine the appropriateness of GABA-based therapeutic approaches to ASD.

There are several limitations to this research that must be considered when interpreting these findings. Perhaps most importantly, the current paradigm allows measurement of cortical inhibition within the motor cortices, but this does not necessarily inform as to cortical inhibition in other brain regions (e.g., prefrontal cortex). It is possible that GABAergic deficits in ASD, as broadly defined, only exist in specific brain regions, such as those identified in histological studies. Future TMS studies in this population should adopt a combined TMS–EEG approach, which has been successfully used to measure cortical inhibition in non-motor sites (Daskalakis et al., 2008; Fitzgerald et al., 2008). Some of the clinical participants were medicated, which may have an effect on our EMG measures. Based on the medication types, however, it seems fairly unlikely that medications would have served to have a significant effect on GABAergic function. As indicated in Table 2, there was also an even split between ASD-LD and ASD-ND with respect to medications that might be expected to modulate measures of GABAergic function (i.e., benzodiazepines and antipsychotics; Daskalakis et al., 2002). In addition, the sample comprised adolescents and adults, and any deficits may be more pronounced among younger samples. Sub-analyses (i.e., ASD-LD vs. ASD-ND) were characterised by relatively small sample sizes, and it is possible that several analyses were underpowered (particularly RH SICI and CSP measures). The use of only 'high-functioning' participants limits generalisability; although there are additional considerations in attempting to include individuals with concurrent intellectual disability (e.g., capacity to provide informed consent, tolerability of TMS), it remains that we cannot gain a full understanding without including these individuals in research projects. Finally, the administration of the various TMS paradigms might be considered repetitive TMS, which can affect corticospinal excitability (and therefore the measured obtained). We consider this unlikely, however, as there was a relatively small number of pulses administered to each hemisphere (55 single pulses, 45 paired pulses), and short breaks implemented between the various paradigms. In addition, stimulation at less than 1 Hz has not been found to consistently affect cortical excitability.

In summary, the current study indicates that GABAergic deficits may not be common to all individuals with high-functioning ASD, but do affect a subset of these individuals (i.e., those with early language delay). Future studies (e.g., TMS–EEG, MRS) will allow us to determine the larger extent and functional relevance of these impairments, and assess whether GABAergic agonists might be of some utility in the treatment of some forms of ASD.

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