Neuroscience

GABA-ergic inhibition in human MT predicts visuo-spatial intelligence mediated by reverberation with frontal cortex

Yuan Gao, Yong-Chun Cai, Dong-Yu Liu, Juan Yu, Jue Wang, Ming Li, Bin Xu, Teng-Fei Wang, Gang Chen, Georg Northoff, Ruiliang Bai, Xue Mei Song

Department of Neurosurgery of the Second Affiliated Hospital and Interdisciplinary Institute of Neuroscience and Technology, Zhejiang University School of Medicine, Hangzhou 310029, China • Department of Psychology and Behavioral Sciences, Zhejiang University, Hangzhou 310028, China • Key Laboratory of Biomedical Engineering of Ministry of Education, Qiushi Academy for Advanced Studies, College of Biomedical Engineering and Instrument Science, Zhejiang University, Hangzhou 310027, China • College of Intelligence Science and Technology, National University of Defense Technology, Changsha 410073, China • University of Ottawa Institute of Mental Health Research, University of Ottawa; Ottawa, ON, K1Z 7K4, Canada • Affiliated Mental Health Center & Hangzhou Seventh People's Hospital, Zhejiang University School of Medicine, Hangzhou 310013, China • MOE Frontier Science Center for Brain Science & Brain-Machine Integration, Zhejiang University, Hangzhou 311121, China

Reviewed Preprint

Published from the original preprint after peer review and assessment by eLife.

About eLife's process

Reviewed preprint version 1
May 17, 2024 (this version)

Posted to preprint server
March 22, 2024

Sent for peer review
March 20, 2024

Abstract

The canonical theory emphasizes fronto-parietal network (FPN) is key in mediating general fluid intelligence (gF). Meanwhile, recent studies show that multiple sensory regions in occipito-temporal border also play a key role in gF. However, the underlying mechanism is not yet clear. To investigate this issue, this study selects human MT complex (MT+), a region locates at the occipito-temporal border representing multiple sensory flows as a target brain area. Using ultra-high field magnetic resonance spectroscopy (MRS) to measure GABA/glutamate concentrations in MT+ combining resting-state fMRI functional connectivity (FC), behavioral examinations including MT+ perception suppression test and gF subtest in visuo-spatial component, we reveal that MT+ GABA and frontal-MT+ FC significantly correlate with the performance of visuo-spatial intelligence. Further, serial mediation model demonstrates that MT+ GABA predicting visuo-spatial *g*F fully mediated by reverberation effect between frontal and MT+ network. Our finding highlights that sensory cortex could integrate into complex cognition system as an intellectual hub.

eLife assessment

This study employed a comprehensive approach to examining how the MT+ region integrates into a complex cognition system in mediating human visuo-spatial intelligence. While the findings are **useful**, the experimental evidence is **incomplete** and the study design, hypothesis, analyses, writing, and presentation need to be improved. The work will be of interest to researchers in psychology, cognitive science, and neuroscience.

Introduction

General fluid intelligence (gF) is a current problem-solving ability, which shows high inter-individual differences in humans(Cattell & Raymond, 1963). At the beginning of the last century, Spearman(Spearman, 1904) proposed that some general or g factor contributes to our cognition. Visuo-spatial intelligence, usually tested by visual materials, is considered to have high g-loading(Colom et al., 2006; Deary et al., 2010; Jung & Haier, 2007). Recently, Duncan et al. show coding of gF in distributed regions including a new multiple-demand (MD) core, the multiple sensory regions at the temporo-occipital border(Assem et al., 2020; Duncan et al., 2020). However, more evidence is needed to uncover how the sensory cortex is a genuine cognitive core. The human extrastriate cortical region, middle temporal complex (MT+), locates at the temporo-occipital border(Dumoulin et al., 2000), and is a key region in the multiple representations of sensory flows (including optic, tactile, and auditory flows)(Bedny et al., 2010; Ricciardi et al., 2007); this ideally suits it to be a new MD core. To further investigate this issue, this work conducted multi-level examination including biochemical (glutamatergic - gabaergic in MT+), regional-systemic (brain connectivity with MT+ - based), and behavioral (visual motion function in MT+) levels to reveal if the function of MT+ contributes to the visuo-spatial component of gF.

Using a well-known visual motion paradigm (center-surround antagonism)(Liu et al., 2016; Tadin et al., 2003), Melnick et al found a strong link between suppression index (SI) of motion perception and the scores of the block design test (BDT, a subtest of the Wechsler Adult Intelligence Scale (WASI), which measures the visuo-spatial component (3D domain) of gF (Melnick et al., 2013). Based on these findings, MT+ is likely to play a key role in MD system of gF. Strong connectivity between the core regions suggests a mechanism for large-scale information exchange and integration in the brain(Barbey, 2018; Cole et al., 2012). This potential conjunctive coding may overlap with the inhibition and/or excitation mechanism of MT+. Taken together, we hypothesized that 3D visuo-spatial intelligence (the performance of BDT) might be predicted by the inhibitory and/or excitation mechanisms in MT+ and the integrative functions connecting MT+ with frontal cortex (**Figure 1a**). To verify the specificity of MT+, we used primary visual cortex (V1) - based GABA/Glu as control as it mediates the 2D rather than 3D visual domain(Born & Bradley, 2005).

We employ ultra-high field (7T) magnetic resonance spectroscopy (MRS) technology to reliably resolve GABA and Glu concentrations(Ende, 2015; Liu et al., 2022; Song et al., 2021), and first demonstrate GABAergic inhibition mechanisms (but not excitatory Glu) in MT+ region involve in the 3D visuo-spatial ability. Further, analysis of functional brain connectivity at rest reveals that the network (between MT+ and frontal cortex) relating to MT+ GABA and perceptual suppression contribute the visuo-spatial intelligence. Our results provide direct evidence that inhibitory mechanisms centered on GABA levels in MT+ region (a sensory cortex) mediate multi-level visuo-spatial component (3D domain) of gF thus drawing a direct connection of biochemistry, brain connectivity, and behavioral levels.

Results

To determine whether the function of MT+ cortex contributes to visuo-spatial component (3D domain) of gF, we adopted the experimental design depicted in **Figure 1b**. Participants underwent two MRI sessions: the first encompassing resting-state fMRI and magnetic resonance spectra (MRS), and the second solely involving MRS. A 30-minute interval separated these sessions, during which participants performed motion discrimination tasks (using center-surround antagonism stimuli)(Tadin et al., 2003) and the block design test (BDT), which assesses the visuo-

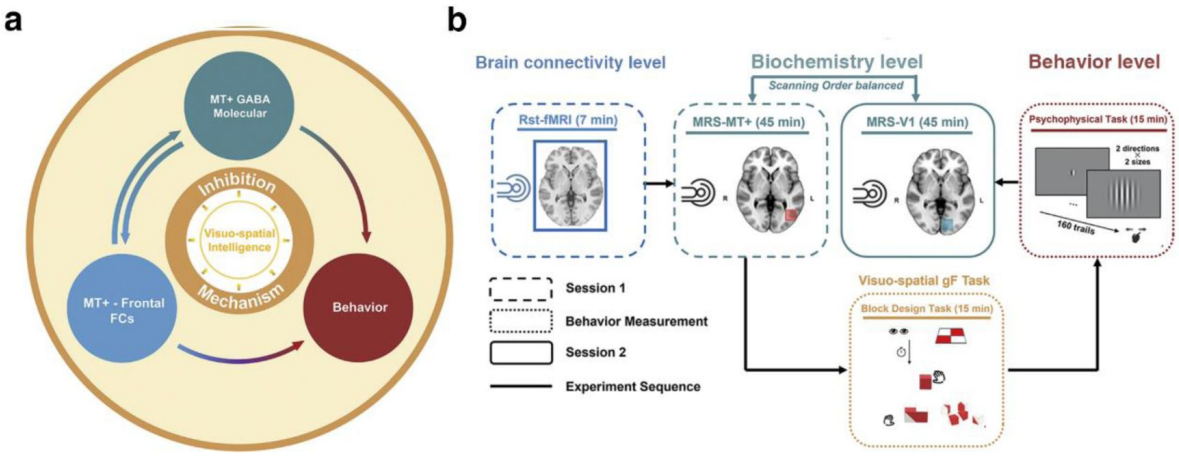

Figure 1.

A priori hypothesis and experimental design. (**a)** Schematic of *a priori* hypothesis. The inhibition mechanism centered on MT+ GABA, including molecular level - the GABAergic inhibition in MT+ (green circle), brain connectivity of MT+ - frontal relating to MT+ GABA (blue circle), and perceptual suppression of visual motion (the behavioral presentation of MT+ function, red circle), contributes to the visuo-spatial component of gF (3D domain, yellow circle). (**b)** Schematic of experimental design. Session 1 (rectangle box of short line) was the functional MRI and MRS scanning at resting state. Session 2 (rectangle box of solid line) was another region of MRS acquisition. In the two sessions, the order of MRS scanning regions (MT+ and V1) was counter balanced across participants. There was a structure MRI scanning before each MRS data acquisition. Interval between the two sessions was used for behavioral measurement (rectangle box of dotted line): block design task (BDT) and psychophysical task - motion discrimination. Sold lines indicate the experiment sequence.

spatial ability (3D domain) of gF(Fangmeier et al., 2006). Both the volume-of-interests (VOIs) of MRS scanning in the left MT+ (targeted brain area) and the left primary visual cortex (V1, control brain area) had dimensions of 2×2×2 cm^3, and the MRS scanning sequences were randomized across the two sessions. The MT+ MRS VOIs were demarcated using an anatomical landmark(Dumoulin et al., 2000). For 14 subjects, we also utilized fMRI to functionally pinpoint the MT+ to validate the placement of the VOI (**Figure 2a, b**). The V1 MRS VOIs were anatomically defined (Methods). Here, MRS data after extensive quality control (31/36 in MT+, and 28/36 in V1) were taken for further analysis (Methods).

GABA and Glu concentrations in MT+ and V1 and their relation to SI and BDT

An example of MRS from voxel located in MT+ is shown in **Figure 3a**. LCModel fittings for GABA spectra from all subjects in MT+ (n = 31) and V1 (n = 28) are illustrated in **Figure 3b** (color scale presents the BDT scores). We discerned a significant association between the inter-subjects' BDT scores and the GABA levels in MT+ voxels, but not in V1 voxels. Quantitative analysis displayed that BDT significantly correlates with GABA concentrations in MT+ voxels (r = 0.39, P = 0.03, n = 31, **Figure 3c**). After using partial correlation to control for the effect of age, the relationship remains significant ($r_{partial}$ = 0.43 P = 0.02, 1 participant excluded due to the age greater than mean + 2.5SD) In contrast, there was no obvious correlation between BDT and GABA levels in V1 voxels (**figure supplement 1a**). We show that SI significantly correlates with GABA levels in MT+ voxels (r = 0.44, P = 0.01, n = 31, **Figure 3d**). In contrast, no significant correlation between SI and GABA concentrations in V1 voxels was observed (**figure supplement 1b**). This finding supports the hypothesis that motion perception is associated with neural activity in MT+ area, but not in V1(Schallmo et al., 2018). LCModel fittings for Glu spectra from all subjects in MT+ (n = 31) and V1 (n = 28) voxels are presented in **figure supplement 2a**.

Unlike in the case of GABA, no significant correlations between BDT and Glu levels were found in both MT+ and V1 voxels (**figure supplement 2b, c**). While, as expected(Song et al., 2021), we observed significant positive correlations between GABA and Glu concentrations in both MT+ (r = 0.62, P < 0.001, n = 31) and V1 voxels (r = 0.56, P = 0.002, n = 28) (**figure supplement 3a, b**). Additionally, a significant correlation between SI and BDT was discerned (r = 0.51, P = 0.002, n = 34, **figure supplement 4a**, $r_{partial}$ = 0.67, P < 0.001, 1 participant excluded due to the age greater than mean + 2.5SD), corroborating previous conclusions(Melnick et al., 2013). Two outliers evident in **Figure 3d** were excluded, with consistent results depicted in **figure supplement 4b**.

MT - frontal FC relates to SI and BDT

We next took the left MT+ as the seed region and separately measured interregional FCs between the seed region and each voxel in the frontal regions (a priori search space). These measurements were correlated with performance in 3D visuospatial ability (BDT) to identify FCs with significant correlations. Results from connectivity-BDT analysis are summarized in **Table 1** and shown in **Figure 4a**. We found that brain regions with FC strength to the seed region (left MT+) significantly correlated with BDT scores were situated within the canonical cognitive cores of MD system or FPN (Brodmann areas (BAs) 6, 9, 10, 46, 47)(Assem et al., 2020; Deary et al., 2010; Duncan et al., 2020; Duncan et al., 2000; Gray et al., 2003; Jung & Haier, 2007). Across the whole brain search, the similar FCs (between MT+ and frontal cognitive cores) still showed significant correlations with BDT scores (**Table supplement 1**) (also shown in **figure supplement 5a**). Additionally, we identified certain parietal regions (BAs 7, 39, 40) with significant correlations between their connectivity to the left MT+ and the BDT scores (**Table supplement 1**) (also shown in **figure supplement 5a**). These significant connections between MT+ and FPN/MD system suggest that left MT+ is involved in the efficient information integration network, serving as a maker of intellectual hub.

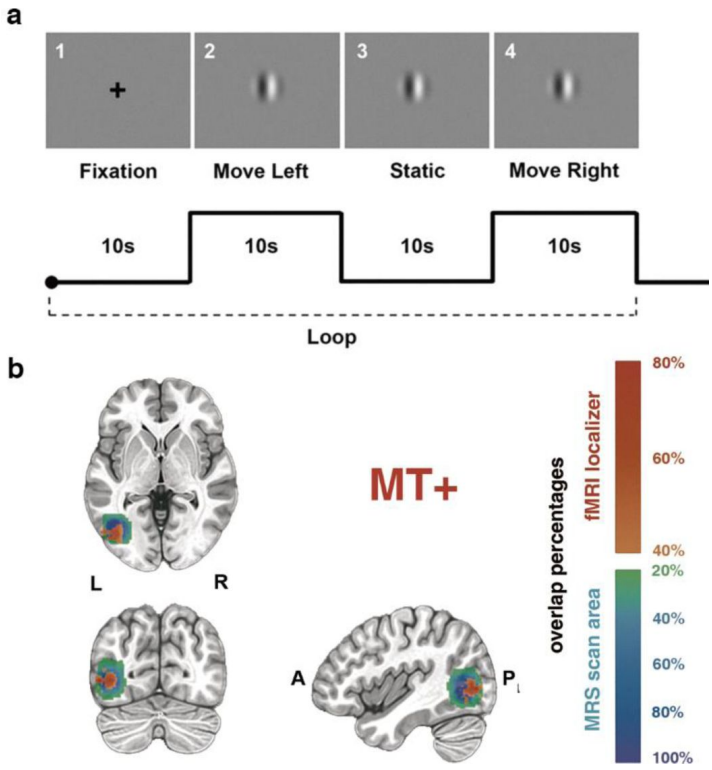

Figure 2.

MT+ localizer scans and MT+ MRS VOI placement. **(a)** Single task block designs. First: a cross fixation on the center of the screen (10s). Second: a moving grating (2°) toward left last 10s. Third: the grating keeps static for 10s. Fourth: the grating moves toward right last 10s. The localizer scans consist of 8 blocks. (**b)** MT+ location and MRS VOI placement. The upper template is the horizontal view. The lower templates from left to right are coronal and sagittal views. The warm color indicates the overlap of fMRI activation of MT+ across 14 subjects, the cold color bar indicates the overlap of MRS VOIs across all subjects.

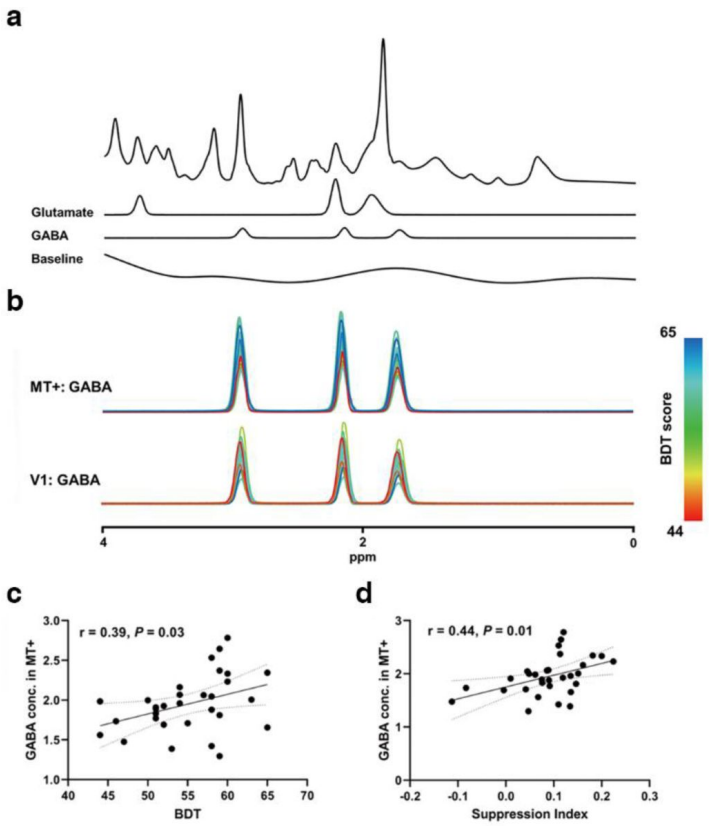

Figure 3.

MRS spectra and the relationships between GABA levels and SI / BDT. (**a)** Example spectrum from the MT+ voxel of one participant. The first line is the LCModel fitting result of all metabolites, and the following lines show the Glu and GABA spectra fitting with LCModel, and then the baseline. (**b)** Individual participants fitted GABA MRS spectra from the MT+ (top) and V1 (bottom) voxels from baseline measurement. The colors of the GABA spectra represent the individual differences of BDT. The color bar represents the scores of BDT. (**c) and (d)** Pearson's correlations showing significant positive correlations between MT+ GABA and BDT scores (**c**), between MT+ GABA and SI (**d**). The ribbon between dotted lines represents the 95% confidence interval, and the black regression line represents the Pearson's correlation coefficient (*r*). GABA and Glu concentrations (Conc.) are absolute, with units of mmol per kg wet weight (Methods).

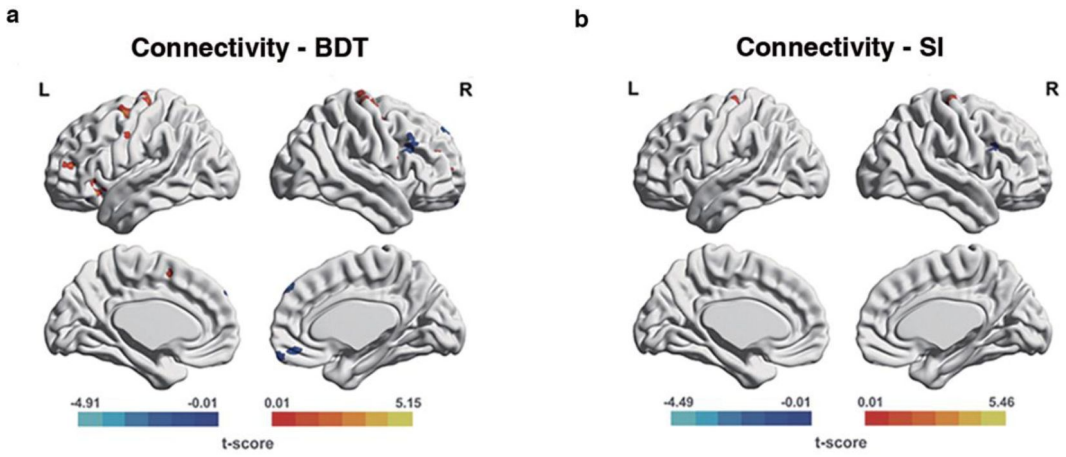

Figure 4.

Significant FCs from connectivity-behavior analyses in *a priori* search space. The seed region is the left MT+. The significant FCs are obtained from *a priori* space (frontal cortex). (**a)** The significant FCs obtained from connectivity-BDT analysis. Single voxel threshold $P < 0.005$, adjacent size ≥ 23 (*AlphaSim* correcting, Methods). (**b)** The significant FCs obtained from connectivity-SI analysis. Single voxel threshold $P < 0.005$, adjacent size ≥ 22 (*AlphaSim* correcting, Methods). Positive correlations are shown in warm colors, while, negative correlations are shown in cold colors.

FC number	Connected regions	BA	Size	Peak coordinate MNI (*x, y, z*)	*r*	*P*
1	Frontal_Sup_Orb_R	11	33	(12,63, -19.5)	-0.57	0.0011
2	Frontal_Inf_Orb_L	47	24	(-34.5,28.5, -13.5)	-0.63	0.0003
3	Frontal_Med_Orb_R	11	41	(3,43.5, -12)	-0.58	0.0009
4	Frontal_Inf_Orb_R	47	48	(-31.5,24, -12)	0.59	0.0008
5	Frontal_Inf_Orb_R	47	29	(25.5,30, -13.5)	0.67	0.0001
6	Insula_L	\	26	(-28.5,27,0)	0.67	0.0001
7	Frontal_Inf_Oper_R	45	41	(43.5,16.5,6)	0.64	0.0002
8	Frontal_Sup_R	10	25	(31.5,57,9)	0.59	0.0008
9	Frontal_Mid_L	10	82	(-33,48,12)	0.62	0.0003
10	Frontal_Inf_Oper_R	44	49	(51,7.5,21)	0.59	0.0007
11	Frontal_Inf_Oper_R	46	96	(49.5,16.5,28.5)	-0.62	0.0003
12	Frontal_Mid_L	10	32	(-31.5,49.5,24)	0.57	0.0012
13	Frontal_Mid_R	10	102	(31.5,36,30)	0.59	0.0009
14	Precentral_L	6	46	(-49.5, -1.5,34.5)	0.59	0.0007
15	Frontal_Mid_R	9	107	(51,19.5,40.5)	-0.67	0.0001
16	Frontal_Sup_L	9	35	(-9,60,37.5)	-0.69	0.0001
17	Frontal_Sup_Medial_R	9	74	(4.5,52.5,43.5)	-0.57	0.0011
18	Frontal_Sup_R	6	136	(28.5, -7.5,63)	-0.64	0.0002
19	Supp_Motor_Area_L	6	48	(-10.5,6,54)	0.63	0.0003
20	Frontal_Mid_L	6	119	(-24,4.5,55.5)	0.63	0.0003
21	Precentral_L	6	229	(-24, -18,66)	0.60	0.0005
22	Frontal_Sup_R	6	32	(16.5, -18,67.5)	0.68	0.0001
23	Precentral_R	6	80	(30, -24,70.5)	0.70	0.0001
24	Precentral_R	6	23	(16.5, -25.5,76.5)	0.70	0.0001

Single voxel threshold $P < 0.005$ ($t > 3.057$ or $t < -3.057$), adjacent size ≥ 23 voxels (AlphaSim corrected).

Table 1.

FC of voxels showing significant correlation with BDT scores across subjects in frontal cortex.

Then, we correlated MT+ - based global FCs with SI. Though spatial suppression during motion perception (quantified by SI) is considered to be the function of area MT+(Melnick et al., 2013), the top-down modulation from the frontal cortex can increase surround suppression(Liu et al., 2016). Our connectivity-SI analysis in the frontal regions (a priori search space) displayed 3 brain regions in which FCs strength significantly correlated with SI: right BA4/6, left BA6, and right BA46 (summarized in **Table supplement 2**, and shown in **Figure 4b**). Across the whole brain search, we identified total 7 brain regions in which FCs strength significantly correlated with SI, and 3 of these were in the frontal cortex. This is consistent with the results obtained by connectivity-SI analysis in a priori search space (frontal cortex) (**Table supplement 3** and **figure supplement 5b**).

Local MT+ GABA acts on SI and BDT via global MT-frontal connectivity

To determine whether local neurotransmitter levels (such as GABA and Glu) in the MT+ region mediate the broader 3D visuo-spatial ability of BDT, which as a component of gF, is linked to the frontal cortex(Fangmeier et al., 2006), we correlated the significant FCs of MT – frontal in **Figure 4a** (also shown in **Table 1**) with the GABA and Glu levels in MT+ region. The results revealed that only two FCs significantly correlated with inhibitory GABA levels in MT+: 1) the FC of left MT+ - right BA 46 (significantly negative correlation, r = - 0.56, P = 0.02, n = 29, FDR correction, **Figure 5a** left); 2) the FC of left MT+ - right BA 6 (significantly positive correlation, r = 0.69, P = 0.002, n = 29, FDR correction, **Figure 5b** left) (also shown in **Table 2**). There were no significant correlations between these FCs and the excitatory Glu levels in MT+ (**Table 2**). Across the whole brain search, we obtained the same two MT+ - frontal FCs significantly correlating with both MT+ GABA levels and BDT (**Table supplement 4**), this is consistent with the results in a priori search space (frontal cortex) (**Table 2**). We then correlated the significant FCs in **Figure 5b** (also in **Table supplement 2**) with GABA and Glu concentrations in MT+ and found that almost all the correlations are significant except one (between the FC of left MT+ - right BA46 and the Glu levels in MT+) (**Table supplement 5**). Among the three FCs, the clusters of two FCs have substantial voxel overlap with the FCs we found by the connectivity-BDT analysis (**Figure 5a, b**). Across the whole brain search, there were total 7 brain regions in which FCs strength were significantly correlated with SI, all the 7 FCs significantly correlated the MT+ GABA levels, while, no FC had significant correlation with the MT+ Glu levels (**Table supplement 6**). Taken together, our results displayed that the overlap FCs from the analyses of connectivity - behavior (BDT and SI)-GABA are the MT+ - BA 46 and MT+ - BA 6 (**Figure 5a, b**). These results suggest that the FCs of MT+ - frontal regions (BA 46 and BA 6) coupling with local MT+ GABA underlie the neural basis for both the simple motion perception (quantified by SI) and the complex 3D visuo-spatial ability (quantified by BDT).

In order to fully investigate the potential roles of multivariable contributing to BDT scores, serial mediation analyses(Hayes, 2013) were applied to the MR and behavioral data. Following our hypothesis, the independent variable (X) is MT+ GABA, the dependent variable (Y) is BDT scores, the covariate is the age, and the mediators are FC (M1) and SI (M2). We used the overlap clusters from the analyses of connectivity-BDT-GABA and connectivity-SI-GABA to compute the FC of MT+ - BA46, 1 participant was excluded due to his age greater than mean + 2.5SD. The serial mediation model is shown in **Figure 5c**. GABA levels in MT+ significantly negatively correlated with the FC of MT+ - BA46 (β = - 0.32, P < 0.001), which in turn significantly negatively correlated with SI (β = - 0.19, P = 0.035), and consequently, significantly positively correlated with BDT (β = 38.5, P = 0.009). Critically, bootstrapped analyses revealed that our hypothesized indirect effect (i.e., MT+ GABA → FC of MT+ - BA46 → SI → BDT) was significant (β = 2.28, SE = 1.54, 95% CI = [0.03, 5.94]). The model accounted for 34% of the variance in BDT. However, when considering the MT-BA6 FC as the mediator M1, the serial model does not show a significant indirect effect. Consequently, we explored a mediation model, which revealed that the MT-BA6 FC totally mediates the relationship between GABA and BDS. (**Figure 5d**). For sensitivity purposes, we tested the alternative models,

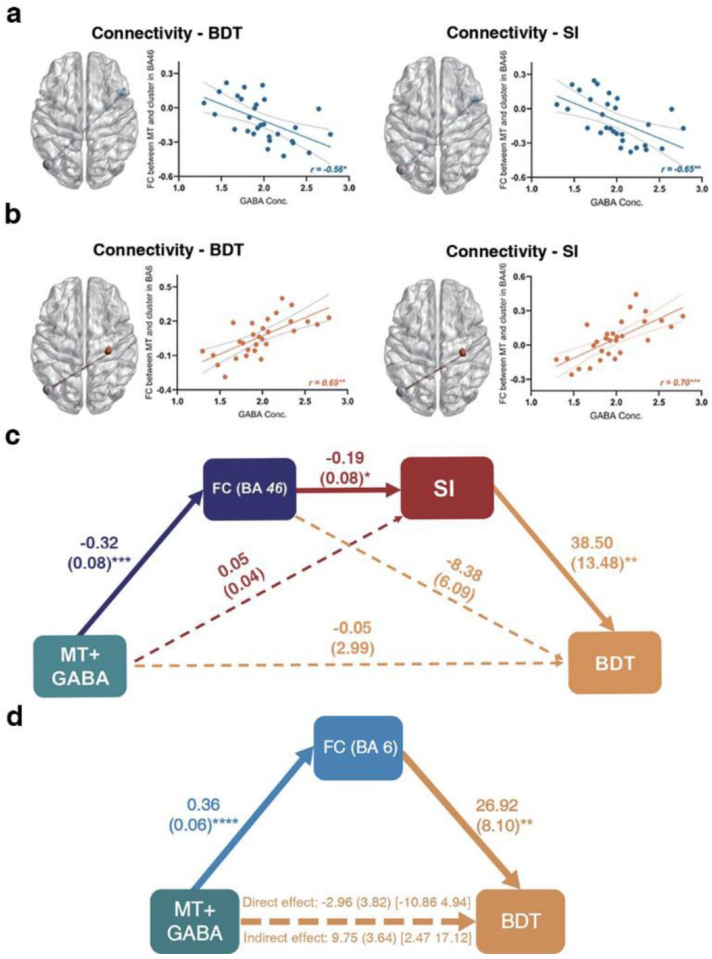

Figure 5.

Local MT+ GABA acts on SI and BDT via global MT-frontal connectivity. (**a)** Significant negative correlation between the FC of left MT+ - right DLPFC (BA46) and MT+ GABA (*FDR* correction). (**b)** Significant positive correlation between the FC of left MT+ - right (pre) motor cortex (BA4/6) and MT+ GABA (*FDR* correction). In (**a)** and (**b)**, left: the significant FCs obtained from connectivity-BDT analysis; right: the significant FCs obtained from connectivity-SI analysis. (**c)** Significant pathways: MT+ GABA→ FC (left MT+ - right BA46, negative correlation) → SI (negative correlation) → BDT (positive correlation). This pathway can explain 34% of the variance in BDT. (**d)** Significant pathways: MT+ GABA → FC (left MT+ - right BA6, positive correlation) → BDT (positive correlation).The bolded lines represent the hypothesized mediation effect. The dotted lines represent alternative pathways. *: P < 0.05; **: P < 0.01; ***: P < 0.001.

FC number	MT+ GABA concentrations			MT+ Glu concentrations		
	r	*P*	***FDR***	*r*	*P*	***FDR***
1	-0.07	0.72	0.75	-0.11	0.58	0.85
2	-0.28	0.14	0.36	-0.27	0.15	0.81
3	-0.13	0.52	0.59	-0.07	0.71	0.85
4	0.10	0.59	0.64	0.12	0.54	0.85
5	0.14	0.48	0.58	0.24	0.21	0.81
6	0.31	0.11	0.33	0.15	0.43	0.85
7	0.20	0.30	0.48	0.07	0.74	0.85
8	0.14	0.45	0.58	0.05	0.79	0.85
9	0.20	0.30	0.48	0.10	0.60	0.85
10	-0.13	0.49	0.58	-0.16	0.41	0.85
11	**-0.56**	**0.0018**	**0.02***	-0.22	0.25	0.81
12	0.18	0.34	0.51	0.15	0.43	0.85
13	0.20	0.30	0.48	0.05	0.81	0.85
14	0.39	0.04	0.14	0.22	0.24	0.81
15	-0.40	0.03	0.12	-0.21	0.27	0.81
16	-0.27	0.15	0.36	-0.12	0.53	0.85
17	0.17	0.37	0.52	0.06	0.74	0.85
18	0.26	0.18	0.39	0.16	0.40	0.85
19	0.39	0.03	0.12	0.31	0.10	0.81
20	0.01	0.98	0.98	0.14	0.46	0.85
21	0.40	0.03	0.12	0.24	0.21	0.81
22	0.22	0.25	0.48	0.06	0.76	0.85
23	**0.69**	**0.0001**	**0.002****	0.47	0.01	0.24
24	0.41	0.03	0.12	0.001	0.97	0.97

Bold font indicates the significant correlations survived from multi correlation correction.

Table 2.

Correlations between FC in Table 1 and GABA/Glu concentrations in MT+.

in which the order of the mediators was reversed. The pathway that MT+ GABA was predicted to be associated with SI, followed by the FC of MT+ - BA 46, and then BDT, did not yield the chained mediation effects on BDT (**figure supplement 6**).

To summarize (shown in **Figure 6**), the results from the serial mediation analyses are consistent with our hypothesis. That is, higher GABAergic inhibition in MT+ relates to stronger negative FC between MT+ and BA46, leading to enhanced ability for surround suppression (filtering out irrelevant information(Tadin, 2015), ultimately resulting in more efficient visual 3D processing of gF (the higher BDT scores).

Discussion

Here, we provide evidence that MT+ inhibitory mechanisms mediate processing in the visuo-spatial component (3D domain) of gF on multiple levels, that is, from molecular over brain connectivity to behavior. First, this study found that higher MT+ inhibitory GABA levels (but not excitatory Glu) relate to FC between MT+ and BA 46 that contribute to both SI and BDT. Our serial mediation analyses indicate that the inhibitory mechanisms linking to MT+, including GABA levels in MT+ (but not Glu), FCs of MT+ - BA46 coupling with MT+ inhibitory GABA (but not excitatory Glu), and behavior (SI indexing perceptual suppression in MT+) predict the inter-subject variance in the 3D gF task (BDT) (**Figure 5c**). Second, we demonstrate discrete GABAergic inhibition mechanisms in MT+ that mediate the strong FCs between MT+ - frontal regions (BA46 and BA6): significant negative correlation with the FC of MT+ - BA 46 (**Figure 5a**), whereas significant positive correlation with the FC of MT+ - BA 6 (**Figure 5b**). This indicates that different frontal regions, DLPFC (BA 46) and premotor cortex (BA6), contribute uniquely to gF through MT+ - based inhibitory mechanisms.

The goal of our research is to reveal that the inhibitory (not excitatory) mechanism in MT+ contributes to multi-level processing in 3D visuo-spatial ability (BDT). Monkey electrophysiological experiments revealed that selective attention gates the visual cortex, including area MT, effectively suppressing the irrelevant information(Everling et al., 2002; Treue & Maunsell, 1996). These findings aligns with the “neural efficiency” hypothesis of intelligence(Haier et al., 1988), which puts forward the human brain’s ability to suppress the repetition of information. Neural suppression is associated with the balance between excitation and inhibition (EIB), usually represented by covariation between Glutamate and GABA(Ozeki et al., 2009). Here, this study exploited the high spectral resolution afforded by ultrahigh field (7T) MRS to reliably resolve GABA measurement, adequately discriminate the glutamate and glutamine signals, and resolve the high accuracy Glu measurement(Ende, 2015).

This work implemented the MRS scanning in MT+ (3D visual domain) and V1 (2D visual domain) regions and found that MT+ inhibitory GABA (but not excitatory Glu) significantly correlated with BDT, i.e., the higher GABA levels in MT+ (rather than excitatory Glu) relate to higher visual 3D processing (BDT) (**Figure 3c**). We searched the global MT+ - based FCs with the connectivity-BDT analyses (in priori search space and whole brain search to valid), and then, correlated these significant FCs with the GABA and Glu concentrations in MT+, and found two FCs (MT+ - BA46 and MT+ - BA6) significantly correlating with MT+ inhibitory GABA (whereas no FC significantly correlated with MT+ excitatory Glu). Accordingly, our results emphasize the importance of MT+ inhibitory GABA (but not excitatory Glu) in processing the 3D visual-spatial intelligence (BDT). Crucially, a previous study has reported a strong link between motion spatial suppression (SI) and the performance of BDT(Melnick et al., 2013). Our recent human study(Song et al., 2021) and other study’s animal experiments(Ozeki et al., 2009; Sato et al., 2016) demonstrated that the conjoint action of inhibition (GABA) and excitation (Glu) underlies visual spatial suppression.

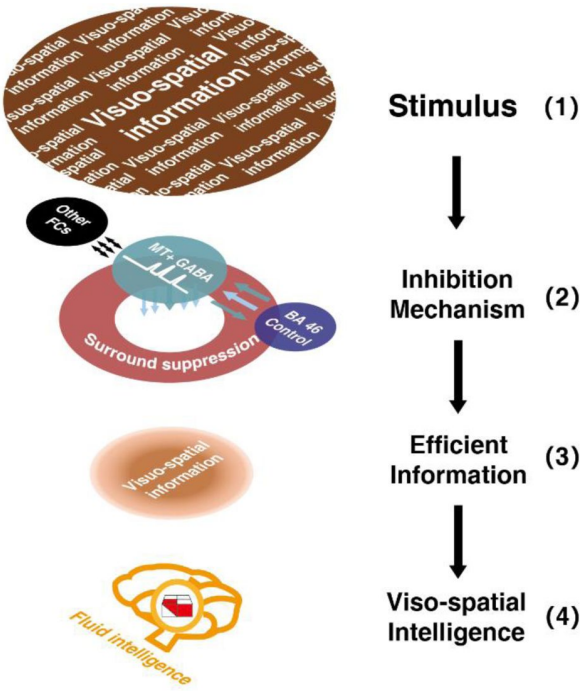

Figure 6.

Sketch depicting the multi-level inhibitory mechanisms centered on MT+ GABA contributing to visuo-spatial intelligence. Inhibitory GABA in MT+ (a sensory cortex, shown in green circle), coupling with the conjunctive coding between MT+ and BA46 (cognitive control core, shown in purple circle), and mediated by motion surround suppression (shown in red circle), contributes to visuo-spatial intelligence (BDT, 3D domain, shown in red and white building blocks). In this sketch, the two-colored parallel arrows show the negative FC between MT+ and BA46, the colored arrows below the green circle display the inhibition mechanisms centered on MT+ GABA (2), filtered the irrelevant information in (1) and focused on the efficient visuo-spatial information (3). Black long arrows display the direction of information flow: from input information (1) to visuo-spatial intelligence (4).

In this work, our novel data show the chained mediation effects from local MT+GABA to more global BDT: MT+ GABA → FC (MT+ and BA46) → SI → BDT. Thereby, our data indicate that inhibitory mechanisms in MT+, from the biochemistry over FC to the behavioral level, can predict the inter-subject variance in the 3D gF task (BDT) (**Figure 5c**).

Another interesting finding reveal that GABAergic inhibition in MT+ coupling with distinct brain connectivity mechanisms between BA 46-MT+ and BA6-MT+. A previous human fMRI experiment found that the positive and negative correlations between BDT and the activation of frontal regions appeared at different reasoning phases (validation or integration phases during reasoning)(Fangmeier et al., 2006). On the one hand, a monkey electrophysiological experiment reported the delayed modulation from PFC (especially in DLPFC (BA 46))) to area MT during a visual motion task(Zaksas & Pasternak, 2006). Computational models converged with empirical data of awake monkey experiments present slow temporal modulation from PFC to MT/MST(Donner et al., 2009; Siegel et al., 2015; Wang, 2002; Wimmer et al., 2015). On the other hand, human MEG studies(Donner et al., 2009; Wilming et al., 2020) reported that the gamma-band activity in the visual cortex (including area MT) exhibited high coherence with the activity in (pre-) motor regions (BA 4/6). These works suggest that the relation of long-range FC and local inhibition mechanism (MT+ GABA) might indicate that inhibition in MT+ contributes to efficient long-range integration and coordination in distant brain areas like the prefrontal and premotor cortex.

How does MT+ assemble into the MD system as an intellectual hub rather than a simple input module? The results in **Figure 5a, c** showed that the overlap brain regions from the analyses of connectivity-BDT-GABA/connectivity-SI-GABA are the MT+ - BA 46. This overlap couples with local visual suppression (SI) and consequently plays an important role in intelligence (BDT). The direction discrimination task in this work (the visual motion paradigm of center-surround antagonism) was previously considered a mainly local function of MT+(Melnick et al., 2013; Tadin, 2015; Tadin et al., 2003). However, our results with connectivity-SI analyses revealed that both local (FC within BA 18) and global brain connectivity (FC between MT+ and frontal regions) contribute to SI (**Table supplement 3**). In human psychophysical experiments(Melnick et al., 2013; Tadin et al., 2003) the brief stimulus duration (~100 ms) in motion discrimination precludes most top-down attentional effects(Wang, 2002; Zaksas & Pasternak, 2006), while, attention, which predicted the performance of the motion discrimination task, was sustained throughout the stimulus intervals(Siegel et al., 2015). Furthermore, animal experiments have revealed that the local circuits in the visual cortex combing with the top-down modulation and intracortical horizontal connection mediate the visual-spatial suppression(Angelucci et al., 2002; Keller et al., 2020; Li et al., 2019; Zhang et al., 2014). Our results (shown in **Figure 5a, b**, right) present the intrinsic binding of local GABAergic inhibition in MT+, which suppressing redundancy of visual motion processing (SI), and the activity of brain connectivity between MT+ and frontal regions. These individually inherent traits may contribute to the individual difference in 3D visuo-spatial ability (**Figure 5a, b**, left). A candidate divisive normalization model(Carandini & Heeger, 2011; Reynolds & Heeger, 2009) can explain how such reverberation affects the process of suppressing the irrelevant information, from perception to intelligence(Melnick et al., 2013; Tadin, 2015). We summarize a framework (**Figure 6**) to indicate and visualize our findings.

Together, this study offers a comprehensive insight into how the information exchange and integration between the sensory cortex (MT+) and cognition core of BA 46, coupling with the MT+ GABA, can predict the performance of 3D visuo-spatial ability (BDT). Our results provide direct evidence that a sensory cortex (MT+), at biochemistry, connectivity, and behavior levels, can assemble into complex cognition as an intellectual hub.

Materials and Methods

Subjects

Thirty-six healthy subjects (18 female, mean age: 23.6 years±2.1, range: 20 to 29 years) participated in this study, they were recruited from Zhejiang University. All subjects had normal or corrected-to-normal vision. In addition, they reported no psychotropic medication use, no illicit drug use within the past month, no alcohol use within 3 days prior to scanning, and right-handed. This experiment was approved by the Ethics Review Committee of Zhejiang University and conducted in accordance with the Helsinki Declaration. All participants signed informed consent forms prior to the start of the study and were compensated for their time. All subjects participated in the motion spatial suppression psychophysical, resting-state fMRI and MRS (MT+ and V1 regions, in random sequence) experiments, but only part of the MRS data (31/36 in MT+ region and 28/36 in V1 region) survived quality control (see the part of MRS date processing). The sample size is determined by the statistic requirement (30 sample for Person correlation statistical analysis).

Motion surrounding suppression measurement

All stimuli were generated using Matlab (MathWorks, Natick, MA) with Psychophysics Toolbox(Brainard, 1997), and were shown on a linearized monitor (1920×1080 resolution, 100-Hz refresh rate, Cambridge Research System, Kent, UK). The viewing distance was 72 cm from the screen, with the head stabilized by a chinrest. Stimuli were drawn against a gray (56 cd per m^{-2}) background.

A schematic of the stimuli and trial sequences is shown in our recent study(Song et al., 2021). The stimulus was a vertical drifting sinusoidal grating (contrast, 50%; spatial frequency, 1 cycle/°; speed, 4°/s) of either small (diameter of 2°) or large (diameter of 10°) size. The edge of the grating was blurred with a raised cosine function (width, 0.3°). A cross was presented in the center of the screen at the beginning of each trial for 500ms, and participants were instructed to fixate at the cross and to keep fixating at the cross throughout the trial. In each trial, a grating of either large or small size was randomly presented at the center of the screen. The grating drifted either leftward or rightward, and participants were asked to judge the perceived moving direction by a key press. Response time was not limited. The grating was ramped on and off with a Gaussian temporal envelope, and the grating duration was defined as 1 SD of the Gaussian function. The duration was adaptively adjusted in each trial, and duration thresholds were estimated by a staircase procedure. Thresholds for large and small gratings were obtained from a 160-trial block that contained four interleaved 3-down/1-up staircases. For each participant, we computed the correct rate for different stimulus durations separately for each stimulus size. These values were then fitted to a cumulative Gaussian function, and the duration threshold corresponding to the 75% correct point on the psychometric function was estimated for each stimulus size.

Stimulus demonstration and practice trials were presented before the first run. Auditory feedback was provided for each wrong response. To quantify the spatial suppression strength, we calculated the spatial suppression index (SI), defined as the difference of log10 thresholds for large versus small stimuli(Schallmo et al., 2018; Tadin et al., 2003):

$$SI = log_{10}(\,large\ threshold) - log_{10}(\,small\ threshold) \qquad (1)$$

Block design task measurement

The block design task was administered in accordance with the WAIS-IV manual(Wechsler, 2008). Specifically, participants were asked to rebuild the figural pattern within a specified time limit using a set of red and white blocks. The time limits were set as 30 s to 120 s according to

different levels of difficulty. The patters were presented in ascending order of difficulty, and the test stopped if two consecutive patterns were not constructed in the allotted time. The score was determined by the accomplishment of the pattern and the time taken. A time bonus was awarded for rapid performance in the last six patterns. The score ranges between 0 and 66 points, with higher scores indicating better perceptual reasoning.

MR experimental procedure

MR experiments were performed in a 7T whole body MR system (Siemens Healthcare, Erlangen, Germany) with a Nova Medical 32 channel array head coil. Sessions included resting-state functional MRI, fMRI localizer scan, structural image scanning, and MRS scan. Resting-state scans were acquired with 1.5-mm isotropic resolution (transverse orientation, TR/TE = 2000/20.6 ms, 160 volumes, slice number = 90, flip angle = 70°, eyes closed). Structural images were acquired using a MP2RAGE sequence (TR/ TI1/ TI2 = 5000/901/3200 ms) with 0.7-mm isotropic resolution. MRS data were collected within two regions (MT+ and V1) for each subject, and we divided them into two sessions to avoid discomfort caused by long scanning. The order of MRS VOIs (MT+ and V1) in the two sessions was counterbalanced across participants. Interval between two sessions was used for block design and motion discrimination tasks. One session included fMRI localizer scan, structural image scanning, and MRS scan for the MT+ region; the other session included structural image scan, and MRS scan for the V1 region. Spectroscopy data were acquired using a ^{1}H-MRS single-voxel short-TE STEAM (Stimulated Echo Acquisition Mode) sequence(Frahm et al., 1989) (TE/TM/TR = 6/32/7100ms) with 4096 sampling points, 4-kHz bandwidth, 16 averages, 8 repetitions, 20×20×20 mm^3 VOI size, and VAPOR (variable power and optimized relaxation delays) water suppression(Tkáč et al., 1999). Prior to acquisition, first- and second-order shims were adjusted using FASTMAP (fast, automatic shimming technique by mapping along projections(Gruetter, 1993). Two non-suppressed water spectra were also acquired: one for phase and eddy current correction (only RF pulse, 4 averages) and another for metabolite quantification (VAPOR none, 4 averages). Voxels were positioned based on anatomical landmarks using a structural image scan collected in the same session, while avoiding contamination by CSF, bone, and fat. The MT+ VOIs were placed in the ventrolateral occipital lobe, which was based on anatomical landmarks(Dumoulin et al., 2000; Schallmo et al., 2018). We did not distinguish between the middle temporal (MT) and medial superior temporal (MST) areas in these MT+ VOIs(Huk et al., 2002). For 14 subjects, we also functionally identified MT+ as a check on the placement of the VOI. A protocol was used with a drifting grating (15% contrast) alternated with a static grating across blocks (10 s block duration, 160 TRs total). Using fMRI BOLD signals, these localizer data were processed online to identify the MT+ voxels in the lateral occipital cortex, which responded more strongly to moving vs. static gratings. In addition, we only used the left MT+ as the target region to scan, which was motivated by studies showing that left MT+ was more effective at causing perceptual effects(Tadin et al., 2011). For V1 region, the VOI was positioned on each subject's calcarine sulcus on the left side(Tadin et al., 2011) based on anatomical landmarks(Boucard et al., 2007; Dumoulin et al., 2000)

MRS data processing

Spectroscopy data were preprocessed and quantified using magnetic resonance signal processing and analysis, *https://www.cmrr.umn.edu/* downloads/mrspa/), which runs under MATLAB and invokes the interface of the LCModel (Version 6.3-1L) (Chen et al., 2019). First, we used the non-suppressed water spectra to perform eddy current correction and frequency/phase correction. Second, we checked the quality of each FID (16 averages) visually and removed those with obviously poor quality. Third, the absolute concentrations of each metabolite were quantitatively estimated via the Water-Scaling method. For partial-volume correction, the tissue water content was computed as follows(Ernst et al., 1993):

$$Tissue\ water\ content = fgm*0.78 + fwm*0.65 + fcsf*0.97 \quad (2)$$

where *fgm*, *fwm*, and *fcsf* were the GM/WM/CSF volume fraction in MRS VOI and we used FAST (fMRI's automated segmentation tool, part of the FSL toolbox)(Zhang et al., 2001) to segment the three tissue compartments from the T1-weighted structural brain images. For water T2 correction, we set water T2 as 47ms (Marjańska et al., 2012). Our concentrations were mM per kg wet weight. Furthermore, LCModel analysis was performed on all spectra within the chemical shift range of 0.2 to 4.0 ppm.

Poor spectral quality was established by a Cramer-Rao Lower Bound (CRLB) of more than 20% (Cavassila et al., 2001), and some data were excluded from further analysis. The details were described in our recently paper(Song et al., 2021).

Rs-fMRI data processing and analysis

Resting-state functional image was analyzed in the Data Processing and Analysis for Brain Imaging DPABI toolbox(Yan et al., 2016) based on SPM 12 (*http://www.fil.ion.ucl.ac.uk/spm/*). The preprocessing steps included discard of the first five volumes, slice timing, realignment to the 90th slice, coregistration of each subject's T1-weighted anatomical and functional images, segmentation of the anatomical images into six types of tissues using DARTEL, linear detrend, regressing nuisance variables (including realignment Friston 24-parameter, global signal, white matter and CSF signal) (Friston et al., 1996), normalization to the standard Montreal Neurological Institute (MNI) space with the voxel size of 1.5× 1.5× 1.5 mm^3 using DARTEL, spatial smoothing with a Gaussian kernel of 3 mm full-width-half-maximum (FWHM), and band-pass filtering with Standard frequency band (SFB, 0.01–0.1 Hz). Spherical ROI with a radius of 6mm was placed in left MT. The coordinate for left MT (−46, −72, −4, in MNI space) was obtained by our localizer fMRI experiment. We calculated the seed-to-voxel whole brain FC map for each subject. All the FC values were Fisher-Z-transformed.

We did a similar connectivity-behavior analysis to a previous study (Song et al., 2008). First, we computed the Pearson's correlation coefficient between BDT scores and the FC values across subjects in a voxel-based way. Then, to evaluate the significance, we transformed the *r*-value into *t*-value $(t = \frac{\sqrt{df}\cdot r}{\sqrt{1-r^2}})$, where *df* denotes to the degrees of freedom, and *r* is the Pearson's correlation coefficient between BDT scores and the FC values. Here, *df* was equal to 27. The brain regions in which the FC values to the seed region was significantly correlated with the BDT scores were obtained with a threshold of $P < 0.005$ for regions of *a priori* ($|t_{(27)}| \geq 3.057$, and adjacent cluster size ≥ 23 voxels (AlphaSim corrected)), and $P < 0.01$ for whole-brain analyses ($|t(27)| \geq 2.771$ and adjacent cluster size ≥ 37 voxels (AlphaSim corrected).

Statistical Analysis

PROCESS version 3.4, a toolbox in SPSS, was used to examine the mediation model. There are some prerequisites for mediation analysis: the independent variable should be a significant predictor of the mediator, and the mediator should be a significant predictor of the dependent variable.

SPSS 20 (IBM, USA) was used to conduct all the remaining statistical analysis in the study. We evaluated the correlation of variables (GABA, Glu, SI, BDT) using Pearson's correlation analysis. Differences or correlations were considered statistically significant if $P < 0.05$. Significances with multiple comparisons were tested with false discovery rate (*FDR*) correction. The effect of age on intelligence was controlled for by using partial correlation in the correlation analysis and was taken as a covariate in the serial mediation model analysis.

Data availability

All data needed to evaluate the conclusions in the paper are present in the paper and/or the Supplementary information. Source data are provided with this paper and have been archived at GitHub. They could be downloaded with reasonable request.

Code availability

This paper does not report original code.

Acknowledgements

The authors thank Prof. Dost Ongur and Fei Du for guidance on the MRS data processing, and thank Zhejiang University 7T Brain Imaging Research Center. This work was supported by STI 2030—Major Projects (2021ZD0200401 to X.M.S., 2022ZD0206000 to R.B.), the National Natural Science Foundation of China Grants (61876222, 32000761, 82222032), Humanities and Social Sciences Ministry of Education (20YJC880095, 18YJA190001), the Key R&D Program of Zhejiang (2022C03096 to X.M.S.), the European Union's Horizon 2020 Framework Program for Research and Innovation under the Specific Grant Agreement No. 785907 (Human Brain Project SGA2 to G.N.), and the MOE Frontier Science Center for Brain Science & Brain-Machine Integration, Zhejiang University.

Author contributions

S.X.M. and Y.G. designed the experiment and G.N. guided the logic of the analysis. Y.G., Y.C. and D.L. conducted human experiments, analyzed data, and Y.G. created figures. R.B. guided the MRI experiments. J.Y., J.W. and B.X. were in charge of data collection and partial date analysis. T. W., M.L. and G.C. guided the data analysis. S.X.M., Y.G. and G.N. wrote the manuscript.

Competing interests

The authors declare no competing interests.

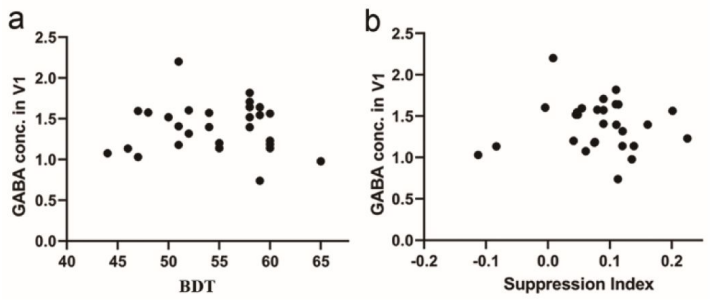

Figure supplement 1.

Relationships between GABA concentration in V1 and BDT/SI. **(a)** There is no significant relationship between BDT and GABA concentrations in V1 region. (**b)** There is also no obvious correlation between SI and GABA concentrations in V1 region. GABA concentration (Conc.) is absolute, with units of mmol per kg wet weight (Methods).

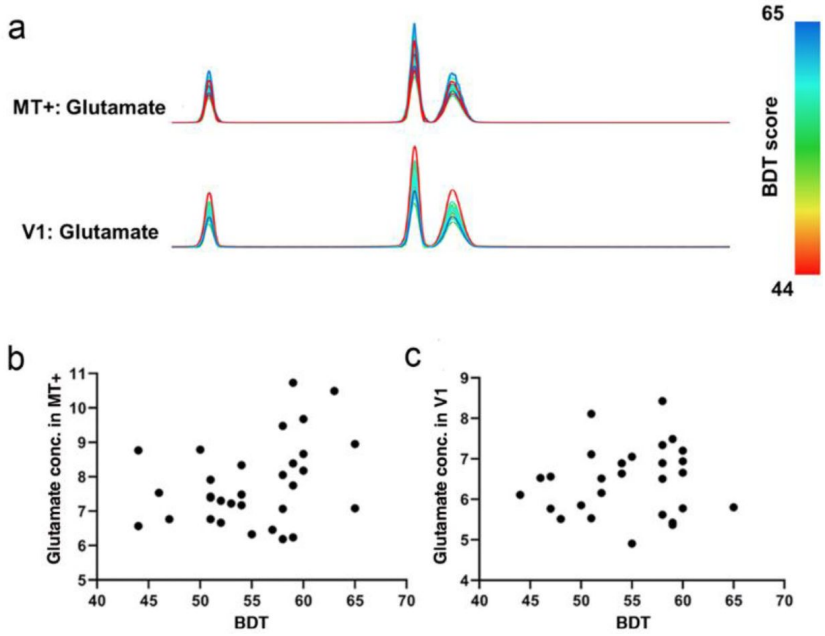

Figure supplement 2.

Individual Glu MRS spectra from MT+ / V1 regions and relationships between BDT and Glu concentrations in MT+ / V1 regions. **(a)** Individual participant fitted Glutamate MRS spectra from the MT+ (top, *n* = 31) and V1 (bottom, *n* = 28) voxels from baseline measurement. The colors of the Glutamate spectra represent the individual differences of BDT. The color bar represents the scores of BDT. (**b)** There is no significant relationship between BDT and Glu concentrations in MT+ region. **c** There is also no significant correlation between BDT and Glu concentrations in V1 region. Glutamate concentration (Conc.) is absolute, with units of mmol per kg wet weight (Methods).

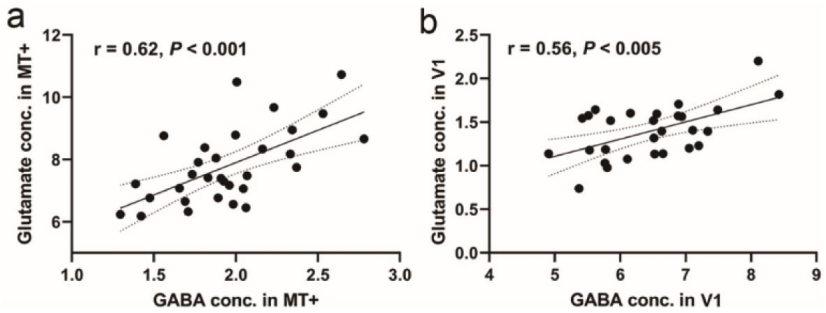

Figure supplement 3.

Correlations between GABA and Glu concentrations in MT+ and V1 regions. **(a)** There is significant correlation between GABA and Glu concentrations in MT+ region. (**b)** The levels of GABA also significantly correlate with Glu in V1 region. GABA and Glu concentrations (Conc.) are absolute, with units of mmol per kg wet weight (Methods).

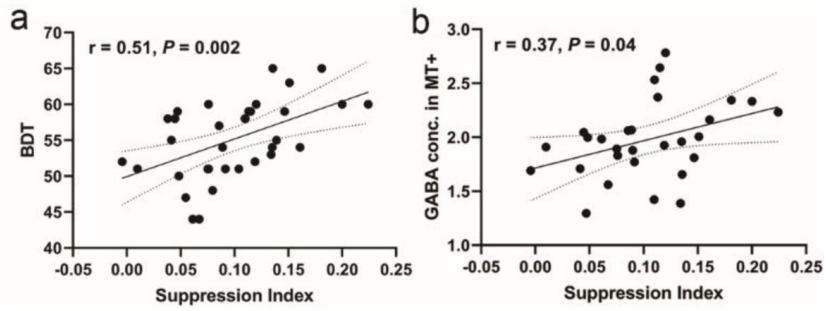

Figure supplement 4.

Two linear correlations. **(a)** Significant positive correlation between suppression index and BDT scores (took out two outlines). (**b)** BDT also significantly correlates with GABA concentration in MT+ region (without two outliers, having the similar result shown in **Figure 2d**).

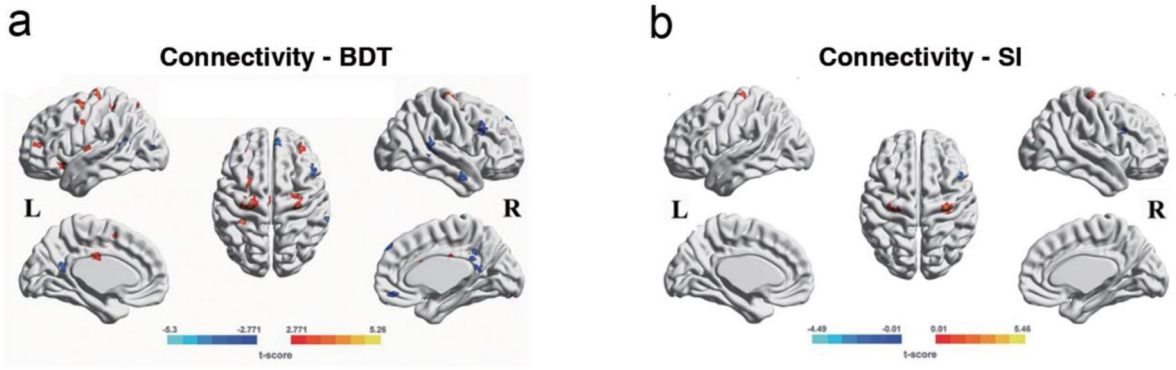

Figure supplement 5.

Significant FCs searched from connectivity-behavior (BDT/SI) analyses in the whole brain. The seed region is the left MT+. The significant FCs are obtained from the entire brain search, single voxel threshold $P < 0.01$, adjacent size ≥ 37 voxels (AlphaSim correcting, Methods). Positive correlations are shown in warm colors, while, negative correlations are shown in cold colors. **(a)** the significant FCs obtained from connectivity-BDT analysis. **(b)** the significant FCs obtained from connectivity-SI analysis.

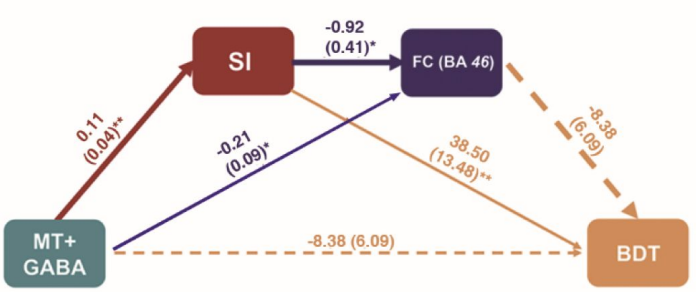

Figure supplement 6.

The alternative serial mediation models from local MT+ GABA to global performance of BDT. The pathway that MT+ GABA was predicted to be associated with SI, followed by the FC of MT+ - BA 46, and then BDT, did not yield the chained mediation effects on BDT. *: P < 0.05; **: < 0.01; ***: P < 0.001.

FC number	Connected regions	BA	Size	Peak coordinate	*r*	*P*
				MNI (*x, y, z*)		
1	Frontal_Med_OrbR	11	44	(2,43.5, -12)	-0.58	0.0009
2	Frontal_Inf_Oper_R	45	49	(43.5,16.5,6)	0.64	0.0002
3	Precentral_L	6	46	(-49.5, -1.5,34.5)	0.59	0.0007
4	Precentral_L	6	237	(-24, -18,66)	0.68	0.0001
5	Precentral_R	6	80	(31, -25,72)	0.67	0.0001
6	Frontal_Mid_L	10	82	(-33,48,12)	0.62	0.0003
7	Insula_L	47	124	(-33,15, -9)	0.64	0.0002
8	Insula_L	13	107	(-31.5,9,10.5)	0.63	0.0002
9	Insula_L	13	44	(-42, -10.5,7.5)	0.64	0.0002
10	Frontal_Inf_Oper_R	44	49	(51,7.5,21)	0.59	0.0007
11	Frontal_Inf_Oper_R	46	96	(49.5,16.5,28.5)	-0.62	0.0003
12	Frontal_Mid_R	10	102	(31.5,36,30)	0.59	0.0009
13	Paracentral_Lobule_L	6	46	(-15,21,51)	-0.64	0.0002
14	Supp_Motor_Area_L	6	48	(-10.5,6,54)	0.63	0.0003
15	Frontal_Mid_L	6	119	(-24,4.5,55.5)	-0.67	0.0001
16	Frontal_Sup_R	6	136	(29, -9,65)	0.57	0.0014
17	Frontal_Sup_MedialR	9	90	(8,51,43)	-0.59	0.0009
18	Frontal_Mid_R	9	108	(50,19,41)	-0.67	0.0001
19	Occipital_Mid_L	19	47	(-43, -83,9)	-0.64	0.0002
20	Occipital_Mid_L	37	45	(-40.5, -63,4.5)	-0.62	0.0004
21	Temporal_Mid_R	39	56	(45, -57,4.5)	-0.71	0.0000
22	Temporal_Mid_L	39	54	(-45, -48,12)	-0.55	0.0021
23	Temporal_Mid_L	40	102	(-48, -55.5,16.5)	-0.65	0.0001
24	Temporal_Mid_R	21	105	(64, -2, -19)	-0.61	0.0004
25	Temporal_Sup_R	22	228	(65, -42,11)	-0.6	0.0006
26	Precuneus_L	30	155	(1.5, -51,16.5)	-0.64	0.0002
27	Cingulum_Ant_R	32	41	(9,15,27)	0.68	0.0000
28	Cingulum_Mid_R	31	73	(15, -46.5,36)	-0.63	0.0002
29	Cingulum_Mid_L	23	80	(-3, -15,30)	0.63	0.0003
30	Lingual_R	18	46	(21, -93, -16)	0.58	0.0009
31	Parietal_Sup_L	7	54	(-19.5, -63,55.5)	0.66	0.0001
32	Parietal_Sup_L	7	48	(-23, -71,58)	0.63	0.0003
33	Postcentral_L	40	41	(-31.5, -39,58.5)	0.68	0.0001
34	Postcentral_L	40	40	(-48, -36,58)	0.71	0.0000
35	Thalamus_L	Wm	108	(-24, -31.5,12)	0.64	0.0002
36	Parietal_Sup_L	5	37	(-37, -48,63)	0.59	0.0008
37	Vermis_10	-	37	(-3, -43, -37)	-0.68	0.0001
38	-	-	40	(12, -19.5, -42)	-0.68	0.0000

Single voxel threshold $P < 0.01$ ($t > 2.771$ or $t < -2.771$), adjacent size ≥ 37 voxels (AlphaSim corrected).

Table supplementary 1.

FC of voxels showing significant correlation with BDT scores across subjects in whole brain.

FC number	Connected regions	BA	Size	Peak coordinate	*r*	*P*
				MNI (*x, y, z*)		
1	Frontal_Inf_Oper_R	46	80	(48,15,28.5)	-0.65	0.0001***
2	Precentral_R	4/6	106	(33, -25.5,63)	0.72	0.0000***
3	Precentral_L	6	26	(-30, -24,72)	0.66	0.0001***

Single voxel threshold $P < 0.005$ (t > 3.057 or t < -3.057), adjacent size ≥ 22 voxels (AlphaSim corrected).

Table supplement 2.

FCs of voxels showing significant correlation with SI across subjects in frontal cortex.

FC number	Connected regions	BA	Size	Peak coordinate	*r*	*P*
				MNI (*x, y, z*)		
1	Cerebelum_Crus1_L	18	70	(-29, -85, -24)	0.51	0.0052
2	Cerebelum_6_R	18	39	(12, -85, -17)	0.65	0.0002
3	Calcarine_R	18	70	(15, -91.5,12)	0.63	0.0003
4	Frontal_Inf_Oper_R	46	127	(48,15,28.5)	-0.65	0.0001
5	Precentral_R	4/6	179	(32, -24,70)	0.71	0.0001
6	Precentral_L	6	59	(-30, -23,72)	0.66	0.0001
7	-	-	37	(26, -37, -11)	-0.67	0.0001

Single voxel threshold $P < 0.01$ (t > 2.771 or t < -2.771), adjacent size ≥ 37 voxels (AlphaSim corrected).

Table supplement 3.

FCs of voxels showing significant correlation with SI across subjects in whole Brain.

FC number	MT+ GABA concentrations			MT+ Glu concentrations		
	r	*P*	***FDR***	*r*	*P*	***FDR***
1	-0.13	0.49	0.55	-0.08	0.68	0.84
2	0.17	0.38	0.49	0.05	0.82	0.88
3	0.39	0.04	0.22	0.22	0.24	0.69
4	0.41	0.03	0.19	0.24	0.21	0.69
5	**0.69**	**0.0001**	**0.0038****	0.47	0.01	0.38
6	0.2	0.3	0.41	0.1	0.6	0.81
7	0.26	0.17	0.34	0.21	0.28	0.69
8	0.22	0.24	0.35	0.25	0.19	0.69
9	0.23	0.23	0.35	0.02	0.9	0.92
10	-0.13	0.49	0.55	-0.16	0.41	0.70
11	**-0.56**	**0.0018**	**0.03***	-0.22	0.25	0.69
12	0.2	0.3	0.41	0.05	0.81	0.88
13	-0.35	0.06	0.25	0.07	0.73	0.84
14	0.39	0.03	0.19	0.31	0.1	0.69
15	0.006	0.98	0.98	0.14	0.46	0.70
16	0.26	0.18	0.34	0.16	0.4	0.70
17	0.15	0.42	0.51	0.04	0.83	0.88
18	-0.4	0.03	0.19	-0.21	0.27	0.69
19	-0.37	0.05	0.24	-0.15	0.44	0.70
20	-0.16	0.39	0.49	-0.19	0.33	0.70
21	-0.31	0.1	0.28	-0.29	0.13	0.69
22	-0.22	0.24	0.35	-0.07	0.72	0.84
23	-0.1	0.6	0.65	-0.12	0.53	0.77
24	-0.09	0.64	0.68	-0.09	0.63	0.83
25	-0.3	0.11	0.28	-0.14	0.46	0.70
26	-0.08	0.66	0.68	-0.08	0.69	0.84
27	0.28	0.13	0.29	0.1	0.59	0.81
28	-0.27	0.16	0.34	-0.2	0.29	0.69
29	0.33	0.08	0.28	0.25	0.19	0.69
30	0.24	0.21	0.35	0.19	0.32	0.70
31	0.24	0.22	0.35	0.36	0.05	0.69
32	0.23	0.24	0.35	0.23	0.23	0.69
33	0.44	0.02	0.19	0.18	0.35	0.70
34	0.32	0.09	0.28	0.002	0.99	0.99
35	0.32	0.09	0.28	0.31	0.1	0.69
36	0.30	0.11	0.28	0.22	0.25	0.69
37	-0.29	0.13	0.29	-0.23	0.23	0.69
38	-0.13	0.48	0.55	-0,15	0.42	0.70

Bold font indicates the significant correlations survived from multi correlation correction.

Table supplement 4.

Correlations between FC in Table supplement 1 and GABA/Glu concentrations in MT+

FC number	MT+ GABA concentrations			MT+ Glu concentrations		
	r	*P*	***FDR***	*r*	*P*	***FDR***
1	**-0.56**	**0.0017**	**0.0017****	-0.21	0.27	0.27
2	**0.70**	**0.0001**	**0.0003*****	**0.49**	**0.007**	**0.021***
3	**0.65**	**0.0001**	**0.0002****	**0.40**	**0.03**	**0.045***

*: $P_{FDR} < 0.05$; **: $P_{FDR} < 0.01$; ***: $P_{FDR} < 0.001$; Bold font indicates the significant correlations survived from multi correlation correction.

Table supplement 5.

Correlations between FCs in Table supplement 2 and GABA/Glu concentrations in MT+.

FC number	MT+ GABA concentrations			MT+ Glu concentrations		
	r	*P*	***FDR***	*r*	*P*	***FDR***
1	**0.37**	**0.049**	**0.049***	0.32	0.09	>0.05
2	**0.37**	**0.049**	**0.049***	0.41	0.025	>0.05
3	**0.48**	**0.008**	**0.01***	0.21	0.28	>0.05
4	**-0.58**	**0.001**	**0.002****	-0.22	0.26	>0.05
5	**0.69**	**0.0001**	**0.0007**	0.46	0.01	>0.05
6	**0.66**	**0.0001**	**0.0004*****	0,39	0.04	>0.05
7	**-0.48**	**0.0077**	**0.01***	-0.35	0.067	>0.05

*: $P_{FDR} < 0.05$; **: $P_{FDR} < 0.01$; ***: $P_{FDR} < 0.001$; Bold font indicates the significant correlations survived from multi correlation correction.

Table supplement 6.

Correlations between FCs in Table supplement 3 and GABA/Glu concentrations in MT+.

References

1. Angelucci A., Levitt J. B., Walton E. J., Hupe J.-M., Bullier J., Lund J. S (2002) **Circuits for local and global signal integration in primary visual cortex** *Journal of Neuroscience* **22**:8633–8646

2. Assem M., Glasser M. F., Van Essen D. C., Duncan J. (2020) **A domain-general cognitive core defined in multimodally parcellated human cortex** *Cerebral Cortex* **30**:4361–4380

3. Barbey A. K (2018) **Network neuroscience theory of human intelligence** *Trends in cognitive sciences* **22**:8–20

4. Bedny M., Konkle T., Pelphrey K., Saxe R., Pascual-Leone A (2010) **Sensitive period for a multimodal response in human visual motion area MT/MST** *Current Biology* **20**:1900–1906

5. Born R. T., Bradley D. C (2005) **Structure and function of visual area MT** *Annu Rev Neurosci* **28**:157–189 https://doi.org/10.1146/annurev.neuro.26.041002.131052

6. Boucard C. C., Hoogduin J. M., van der Grond J., Cornelissen F. W. (2007) **Occipital proton magnetic resonance spectroscopy (1H-MRS) reveals normal metabolite concentrations in retinal visual field defects** *PLoS One* **2**

7. Brainard D. H (1997) **The Psychophysics Toolbox** *Spat Vis* **10**:433–436

8. Carandini M., Heeger D. J (2011) **Normalization as a canonical neural computation** *Nat Rev Neurosci* **13**:51–62 https://doi.org/10.1038/nrn3136

9. Cattell, & Raymond, B (1963) **Theory of fluid and crystallized intelligence: A critical experiment** *Journal of Educational Psychology* **54**:1–22

10. Cavassila S., Deval S., Huegen C., Van Ormondt D., Graveron-Demilly D. (2001) **Cramér–Rao bounds: an evaluation tool for quantitation** *NMR in Biomedicine: An International Journal Devoted to the Development and Application of Magnetic Resonance In Vivo* **14**:278–283

11. Chen X., Fan X., Hu Y., Zuo C., Whitfield-Gabrieli S., Holt D., Gong Q., Yang Y., Pizzagalli D. A., Du F (2019) **Regional GABA concentrations modulate inter-network resting-state functional connectivity** *Cerebral Cortex* **29**:1607–1618

12. Cole M. W., Yarkoni T., Repovs G., Anticevic A., Braver T. S (2012) **Global connectivity of prefrontal cortex predicts cognitive control and intelligence** *J Neurosci* **32**:8988–8999 https://doi.org/10.1523/JNEUROSCI.0536-12.2012

13. Colom R., Jung R. E., Haier R. J (2006) **Distributed brain sites for the g-factor of intelligence** *Neuroimage* **31**:1359–1365 https://doi.org/10.1016/j.neuroimage.2006.01.006

14. Deary I. J., Penke L., Johnson W (2010) **The neuroscience of human intelligence differences** *Nature reviews neuroscience* **11**:201–211

15. Donner T. H., Siegel M., Fries P., Engel A. K (2009) **Buildup of choice-predictive activity in human motor cortex during perceptual decision making** *Curr Biol* **19**:1581–1585 https://doi.org/10.1016/j.cub.2009.07.066

16. Dumoulin S. O., Bittar R. G., Kabani N. J., Baker C. L., Le Goualher G., Bruce Pike G., Evans A. C. (2000) **A new anatomical landmark for reliable identification of human area V5/MT: a quantitative analysis of sulcal patterning** *Cereb Cortex* **10**:454–463 https://doi.org/10.1093/cercor/10.5.454

17. Duncan J., Assem M., Shashidhara S (2020) **Integrated Intelligence from Distributed Brain Activity** *Trends Cogn Sci* **24**:838–852 https://doi.org/10.1016/j.tics.2020.06.012

18. Duncan J., Seitz R. J., Kolodny J., Bor D., Herzog H., Ahmed A., Newell F. N., Emslie H (2000) **A neural basis for general intelligence** *Science* **289**:457–460 https://doi.org/10.1126/science.289.5478.457

19. Ende G (2015) **Proton Magnetic Resonance Spectroscopy: Relevance of Glutamate and GABA to Neuropsychology** *Neuropsychol Rev* **25**:315–325 https://doi.org/10.1007/s11065-015-9295-8

20. Ernst T., Kreis R., Ross B (1993) **Absolute quantitation of water and metabolites in the human brain. I. Compartments and water** . *Journal of magnetic resonance, Series B* **102**:1–8

21. Everling S., Tinsley C. J., Gaffan D., Duncan J (2002) **Filtering of neural signals by focused attention in the monkey prefrontal cortex** *Nature neuroscience* **5**:671–676

22. Fangmeier T., Knauff M., Ruff C. C., Sloutsky V (2006) **fMRI evidence for a three-stage model of deductive reasoning** *Journal of cognitive neuroscience* **18**:320–334

23. Frahm, J. a., Bruhn, H., Gyngell, M., Merboldt, K., Hänicke, W., & Sauter, R (1989) **Localized high- resolution proton NMR spectroscopy using stimulated echoes: initial applications to human brain in vivo** *Magnetic resonance in medicine* **9**:79–93

24. Friston K. J., Williams S., Howard R., Frackowiak R. S., Turner R (1996) **Movement-related effects in fMRI time-series** *Magnetic resonance in medicine* **35**:346–355

25. Gray J. R., Chabris C. F., Braver T. S (2003) **Neural mechanisms of general fluid intelligence** *Nat Neurosci* **6**:316–322 https://doi.org/10.1038/nn1014

26. Gruetter R (1993) **Automatic, localized in vivo adjustment of all first-and second-order shim coils** *Magnetic resonance in medicine* **29**:804–811

27. Haier R. J., Siegel Jr B. V., Nuechterlein K. H., Hazlett E., Wu J. C., Paek J., Browning H. L., Buchsbaum M. S (1988) **Cortical glucose metabolic rate correlates of abstract reasoning and attention studied with positron emission tomography** *Intelligence* **12**:199–217

28. Hayes A. F (2013) **Introduction to Mediation, Moderation, and Conditional Process Analysis: A Regression-Based Approach**

29. Huk A. C., Dougherty R. F., Heeger D. J (2002) **Retinotopy and functional subdivision of human areas MT and MST** *Journal of Neuroscience* **22**:7195–7205

30. Jung R. E., Haier R. J, discussion 154-187 (2007) **The Parieto-Frontal Integration Theory (P-FIT) of intelligence: converging neuroimaging evidence** *Behav Brain Sci* **30**:135–154 https://doi.org/10.1017/S0140525X07001185

31. Keller A. J., Roth M. M., Scanziani M (2020) **Feedback generates a second receptive field in neurons of the visual cortex** *Nature* **582**:545–549

32. Li M., Song X. M., Xu T., Hu D., Roe A. W., Li C.-Y (2019) **Subdomains within orientation columns of primary visual cortex** *Science advances* **5**

33. Liu D. Y., Ju X., Gao Y., Han J. F., Li Z., Hu X. W., Tan Z. L., Northoff G., Song X. M (2022) **From Molecular to Behavior: Higher Order Occipital Cortex in Major Depressive Disorder** *Cereb Cortex* **32**:2129–2139 https://doi.org/10.1093/cercor/bhab343

34. Liu L. D., Haefner R. M., Pack C. C (2016) **A neural basis for the spatial suppression of visual motion perception** *Elife* **5**

35. Marjańska M., Auerbach E. J., Valabrègue R., Van de Moortele P. F., Adriany G., Garwood M. (2012) **Localized 1H NMR spectroscopy in different regions of human brain in vivo at 7 T: T2 relaxation times and concentrations of cerebral metabolites** *NMR in Biomedicine* **25**:332–339

36. Melnick M. D., Harrison B. R., Park S., Bennetto L., Tadin D (2013) **A strong interactive link between sensory discriminations and intelligence** *Curr Biol* **23**:1013–1017 https://doi.org/10.1016/j.cub.2013.04.053

37. Ozeki H., Finn I. M., Schaffer E. S., Miller K. D., Ferster D (2009) **Inhibitory stabilization of the cortical network underlies visual surround suppression** *Neuron* **62**:578–592

38. Reynolds J. H., Heeger D. J (2009) **The normalization model of attention** *Neuron* **61**:168–185

39. Ricciardi, E., Vanello, N., Sani, L., Gentili, C., Scilingo, E. P., Landini, L., Guazzelli, M., Bicchi, A., Haxby, J. V.,, Pietrini (2007) **The effect of visual experience on the development of functional architecture in hMT+** *Cerebral Cortex* **17**:2933–2939

40. Sato T. K., Haider B., Häusser M., Carandini M (2016) **An excitatory basis for divisive normalization in visual cortex** *Nature neuroscience* **19**:568–570

41. Schallmo M. P., Kale A. M., Millin R., Flevaris A. V., Brkanac Z., Edden R. A., Bernier R. A., Murray S. O (2018) **Suppression and facilitation of human neural responses** *Elife* **7** https://doi.org/10.7554/eLife.30334

42. Siegel M., Buschman T. J., Miller E. K (2015) **Cortical information flow during flexible sensorimotor decisions** *Science* **348**:1352–1355 https://doi.org/10.1126/science.aab0551

43. Song M., Zhou Y., Li J., Liu Y., Tian L., Yu C., Jiang T (2008) **Brain spontaneous functional connectivity and intelligence** *Neuroimage* **41**:1168–1176 https://doi.org/10.1016/j.neuroimage.2008.02.036

44. Song X. M. *et al.* (2021) **Reduction of higher-order occipital GABA and impaired visual perception in acute major depressive disorder** *Mol Psychiatry* **26**:6747–6755 https://doi.org/10.1038/s41380-021-01090-5

45. Spearman C (1904) **General Intelligence" Objectively Determined and Measured** *American Journal of Psychology* **15**:201–293

46. Tadin D (2015) **Suppressive mechanisms in visual motion processing: From perception to intelligence** *Vision Res* **115**:58–70 https://doi.org/10.1016/j.visres.2015.08.005

47. Tadin D., Lappin J. S., Gilroy L. A., Blake R (2003) **Perceptual consequences of centre-surround antagonism in visual motion processing** *Nature* **424**:312–315 https://doi.org/10.1038/nature01800

48. Tadin D., Silvanto J., Pascual-Leone A., Battelli L (2011) **Improved motion perception and impaired spatial suppression following disruption of cortical area MT/V5** *Journal of Neuroscience* **31**:1279–1283

49. Tkáč I., Starčuk Z., Choi I. Y., Gruetter R (1999) **In vivo 1H NMR spectroscopy of rat brain at 1 ms echo time** *Magnetic Resonance in Medicine: An Official Journal of the International Society for Magnetic Resonance in Medicine* **41**:649–656

50. Treue S., Maunsell J. H (1996) **Attentional modulation of visual motion processing in cortical areas MT and MST** *Nature* **382**:539–541

51. Wang X. J (2002) **Probabilistic decision making by slow reverberation in cortical circuits** *Neuron* **36**:955–968 https://doi.org/10.1016/s0896-6273(02)01092-9

52. Wechsler D. (2008) **Wechsler, D. (2008). Wechsler Memory Scale–Fourth Edition (WMS-IV) technical and interpretive manual.** *Wechsler Memory Scale–Fourth Edition (WMS-IV) technical and interpretive manual*

53. Wilming N., Murphy P. R., Meyniel F., Donner T. H (2020) **Large-scale dynamics of perceptual decision information across human cortex** *Nat Commun* **11** https://doi.org/10.1038/s41467-020-18826-6

54. Wimmer K., Compte A., Roxin A., Peixoto D., Renart A., de la Rocha J. (2015) **Sensory integration dynamics in a hierarchical network explains choice probabilities in cortical area MT** *Nat Commun* **6** https://doi.org/10.1038/ncomms7177

55. Yan C.-G., Wang X.-D., Zuo X.-N., Zang Y.-F (2016) **DPABI: data processing & analysis for (resting-state) brain imaging** *Neuroinformatics* **14**:339–351

56. Zaksas D., Pasternak T (2006) **Directional signals in the prefrontal cortex and in area MT during a working memory for visual motion task** *J Neurosci* **26**:11726–11742 https://doi.org/10.1523/JNEUROSCI.3420-06.2006

57. Zhang S., Xu M., Kamigaki T., Hoang Do J. P., Chang W.-C., Jenvay S., Miyamichi K., Luo L., Dan Y (2014) **Long-range and local circuits for top-down modulation of visual cortex processing** *Science* **345**:660–665

58. Zhang Y., Brady M., Smith S (2001) **Segmentation of brain MR images through a hidden Markov random field model and the expectation-maximization algorithm** *IEEE transactions on medical imaging* **20**:45–57

Article and author information

Yuan Gao

Department of Neurosurgery of the Second Affiliated Hospital and Interdisciplinary Institute of Neuroscience and Technology, Zhejiang University School of Medicine, Hangzhou 310029, China

Yong-Chun Cai
Department of Psychology and Behavioral Sciences, Zhejiang University, Hangzhou 310028, China

Dong-Yu Liu
Department of Neurosurgery of the Second Affiliated Hospital and Interdisciplinary Institute of Neuroscience and Technology, Zhejiang University School of Medicine, Hangzhou 310029, China, Key Laboratory of Biomedical Engineering of Ministry of Education, Qiushi Academy for Advanced Studies, College of Biomedical Engineering and Instrument Science, Zhejiang University, Hangzhou 310027, China

Juan Yu
Department of Neurosurgery of the Second Affiliated Hospital and Interdisciplinary Institute of Neuroscience and Technology, Zhejiang University School of Medicine, Hangzhou 310029, China, Key Laboratory of Biomedical Engineering of Ministry of Education, Qiushi Academy for Advanced Studies, College of Biomedical Engineering and Instrument Science, Zhejiang University, Hangzhou 310027, China

Jue Wang
Department of Neurosurgery of the Second Affiliated Hospital and Interdisciplinary Institute of Neuroscience and Technology, Zhejiang University School of Medicine, Hangzhou 310029, China

Ming Li
College of Intelligence Science and Technology, National University of Defense Technology, Changsha 410073, China

Bin Xu
Department of Neurosurgery of the Second Affiliated Hospital and Interdisciplinary Institute of Neuroscience and Technology, Zhejiang University School of Medicine, Hangzhou 310029, China

Teng-Fei Wang
Department of Psychology and Behavioral Sciences, Zhejiang University, Hangzhou 310028, China
ORCID iD: 0000-0002-1585-4143

Gang Chen
Department of Neurosurgery of the Second Affiliated Hospital and Interdisciplinary Institute of Neuroscience and Technology, Zhejiang University School of Medicine, Hangzhou 310029, China, Key Laboratory of Biomedical Engineering of Ministry of Education, Qiushi Academy for Advanced Studies, College of Biomedical Engineering and Instrument Science, Zhejiang University, Hangzhou 310027, China, University of Ottawa Institute of Mental Health Research, University of Ottawa; Ottawa, ON, K1Z 7K4, Canada

Georg Northoff
Affiliated Mental Health Center & Hangzhou Seventh People's Hospital, Zhejiang University School of Medicine, Hangzhou 310013, China, University of Ottawa Institute of Mental Health Research, University of Ottawa; Ottawa, ON, K1Z 7K4, Canada
For correspondence: georg.northoff@theroyal.ca

Ruiliang Bai
Department of Neurosurgery of the Second Affiliated Hospital and Interdisciplinary Institute of Neuroscience and Technology, Zhejiang University School of Medicine, Hangzhou 310029, China, Key Laboratory of Biomedical Engineering of Ministry of Education, Qiushi Academy for Advanced Studies, College of Biomedical Engineering and Instrument Science, Zhejiang University, Hangzhou 310027, China, MOE Frontier Science Center for Brain Science & Brain-Machine Integration, Zhejiang University, Hangzhou 311121, China
For correspondence: ruiliangbai@zju.edu.cn

Xue Mei Song
Department of Neurosurgery of the Second Affiliated Hospital and Interdisciplinary Institute of Neuroscience and Technology, Zhejiang University School of Medicine, Hangzhou 310029, China, Key Laboratory of Biomedical Engineering of Ministry of Education, Qiushi Academy for Advanced Studies, College of Biomedical Engineering and Instrument Science, Zhejiang University, Hangzhou 310027, China, Affiliated Mental Health Center & Hangzhou Seventh People's Hospital, Zhejiang University School of Medicine, Hangzhou 310013, China, MOE Frontier Science Center for Brain Science & Brain-Machine Integration, Zhejiang University, Hangzhou 311121, China
For correspondence: songxuemei@zju.edu.cn
ORCID iD: 0000-0003-3624-4245

Copyright

Editors

Reviewing Editor
Xilin Zhang
South China Normal University, Guangzhou, China

Senior Editor
Yanchao Bi
Beijing Normal University, Beijing, China

Reviewer #1 (Public Review):

Summary:

The study of human intelligence has been the focus of cognitive neuroscience research, and finding some objective behavioral or neural indicators of intelligence has been an ongoing problem for scientists for many years. Melnick et al, 2013 found for the first time that the phenomenon of spatial suppression in motion perception predicts an individual's IQ score. This is because IQ is likely associated with the ability to suppress irrelevant information. In this study, a high-resolution MRS approach was used to test this theory. In this paper, the phenomenon of spatial suppression in motion perception was found to be correlated with the visuo-spatial subtest of gF, while both variables were also correlated with the GABA concentration of MT+ in the human brain. In addition, there was no significant relationship

with the excitatory transmitter Glu. At the same time, SI was also associated with MT+ and several frontal cortex FCs.

Strengths:

(1) 7T high-resolution MRS is used.

(2) This study combines the behavioral tests, MRS, and fMRI.

Weaknesses:

(1) In the intro, it seems to me that the multiple-demand (MD) regions are the key in this study. However, I didn't see any results associated with the MD regions. Did I miss something??

(2) How was the sample size determined? Is it sufficient??

(3) In Schallmo elife 2018, there was no correlation between GABA concentration and SI. How can we justify the different results different here?

(4) Basically this study contains the data of SI, BDT, GABA in MT+ and V1, Glu in MT+ and V1- all 6 measurements. There should be 6x5/2 = 15 pairwise correlations. However, not all of these results are included in Figure 1 and supplementary 1-3. I understand that it is not necessary to include all figures. But I suggest reporting all values in one Table.

(5) In Melnick (2013), the IQ scores were measured by the full set of WAIS-III, including all subtests. However, this study only used the visual spatial domain of gF. I wonder why only the visuo-spatial subtest was used not the full WAIS-III?

(6) In the functional connectivity part, there is no explanation as to why only the left MT+ was set to the seed region. What is the problem with the right MT+?

(7) In Melnick (2013), the authors also reported the correlation between IQ and absolute duration thresholds of small and large stimuli. Please include these analyses as well.

https://doi.org/10.7554/eLife.97545.1.sa2

Reviewer #2 (Public Review):

Summary:

Recent studies have identified specific regions within the occipito-temporal cortex as part of a broader fronto-parietal, domain-general, or "multiple-demand" (MD) network that mediates fluid intelligence (gF). According to the abstract, the authors aim to explore the mechanistic roles of these occipito-temporal regions by examining GABA/glutamate concentrations. However, the introduction presents a different rationale: investigating whether area MT+ specifically, could be a core component of the MD network.

Strengths:

The authors provide evidence that GABA concentrations in MT+ and its functional connectivity with frontal areas significantly correlate with visuo-spatial intelligence performance. Additionally, serial mediation analysis suggests that inhibitory mechanisms in MT+ contribute to individual differences in a specific subtest of the Wechsler Adult Intelligence Scale, which assesses visuo-spatial aspects of gF.

Weaknesses:

While the findings are compelling and the analyses robust, the study's rationale and interpretations need strengthening. For instance, Assem et al. (2020) have previously defined the core and extended MD networks, identifying the occipito-temporal regions as TE1m and TE1p, which are located more rostrally than MT+. Area MT+ might overlap with brain regions identified previously in Fedorenko et al., 2013, however the authors attribute these activations to attentional enhancement of visual representations in the more difficult conditions of their tasks. For the aforementioned reasons, It is unclear why the authors chose MT+ as their focus. A stronger rationale for this selection is necessary and how it fits with the core/extended MD networks.

Moreover, although the study links MT+ inhibitory mechanisms to a visuo-spatial component of gF, this evidence alone may not suffice to position MT+ as a new core of the MD network. The MD network's definition typically encompasses a range of cognitive domains, including working memory, mathematics, language, and relational reasoning. Therefore, the claim that MT+ represents a new core of MD needs to be supported by more comprehensive evidence.

https://doi.org/10.7554/eLife.97545.1.sa1

Reviewer #3 (Public Review):

Summary:

This manuscript aims to understand the role of GABA-ergic inhibition in the human MT+ region in predicting visuo-spatial intelligence through a combination of behavioral measures, fMRI (for functional connectivity measurement), and MRS (for GABA/glutamate concentration measurement). While this is a commendable goal, it becomes apparent that the authors lack fundamental understanding of vision, intelligence, or the relevant literature. As a result, the execution of the research is less coherent, dampening the enthusiasm of the review.

Strengths:

(1) Comprehensive Approach: The study adopts a multi-level approach, i.e., neurochemical analysis of GABA levels, functional connectivity, and behavioral measures to provide a holistic understanding of the relationship between GABA-ergic inhibition and visuo-spatial intelligence.

(2) Sophisticated Techniques: The use of ultra-high field magnetic resonance spectroscopy (MRS) technology for measuring GABA and glutamate concentrations in the MT+ region is a recent development.

Weaknesses:

Study Design and Hypothesis
(1) The central hypothesis of the manuscript posits that "3D visuo-spatial intelligence (the performance of BDT) might be predicted by the inhibitory and/or excitation mechanisms in MT+ and the integrative functions connecting MT+ with the frontal cortex." However, several issues arise:
1.1 The Suppression Index depicted in Figure 1a, labeled as the "behavior circle," appears irrelevant to the central hypothesis.
1.2 The construct of 3D visuo-spatial intelligence, operationalized as the performance in the Block Design task, is inconsistently treated as another behavioral task throughout the manuscript, leading to confusion.
1.3 The schematics in Figure 1a and Figure 6 appear too high-level to be falsifiable. It is suggested that the authors formulate specific and testable hypotheses and preregister them before data collection.

(2) Central to the hypothesis and design of the manuscript is a misinterpretation of a prior study by Melnick et al. (2013). While the original study identified a strong correlation between WAIS (IQ) and the Suppression Index (SI), the current manuscript erroneously asserts a specific relationship between the block design test (from WAIS) and SI. It should be noted that in the original paper, WAIS comprises Similarities, Vocabulary, Block design, and Matrix reasoning tests in Study 1, while the complete WAIS is used in Study 2. Did the authors conduct other WAIS subtests other than the block design task?

(3) Additionally, there are numerous misleading references and unsubstantiated claims throughout the manuscript. As an example of misleading reference, "the human MT ... a key region in the multiple representations of sensory flows (including optic, tactile, and auditory flows) (Bedny et al., 2010; Ricciardi et al., 2007); this ideally suits it to be a new MD core." The two references in this sentence are claims about plasticity in the congenitally blind with sensory deprivation from birth, which is not really relevant to the proposal that hMT+ is a new MD core in healthy volunteers.
Another example of unsubstantiated claim: the rationale for selecting V1 as the control region is based on the assertion that "it mediates the 2D rather than 3D visual domain (Born & Bradley, 2005)". That's not the point made in the Born & Bradley (2005) paper on MT. It's crucial to note that V1 is where the initial binocular convergence occurs in cortex, i.e., inputs from both the right and left eyes to generate a perception of depth.

Results & Discussion
(1) The missing correlation between SI and BDT is crucial to the rest of the analysis. The authors should discuss whether they replicated the pattern of results from Melnick et al. (2013) despite using only one WAIS subtest.

(2) ROIs: can the authors clarify if the results are based on bilateral MT+/V1 or just those in the left hemisphere? Can the authors plot the MRS scan area in V1? I would be surprised if it's precise to V1 and doesn't spread to V2/3 (which is fine to report as early visual cortex).

(3) Did the authors examine V1 FC with either the frontal regions and/or whole brain, as a control analysis? If not, can the author justify why V1 serves as the control region only in the MRS but not in FC (Figure 4) or the mediation analysis (Figure 5)? That seems a little odd given that control analyses are needed to establish the specificity of the claim to MT+.

(4) It is not clear how to interpret the similarity or difference between panels a and b in Figure 4.

(5) SI is not relevant to the authors' priori hypothesis, but is included in several mediation analyses. Can the authors do model comparisons between the ones in Figure 5c, d, and Figure S6? In other words, is SI necessary in the mediation model? There seem discrepancies between the necessity of SI in Figures 5c/S6 vs. Figure 5d.

(6) The sudden appearance of "efficient information" in Figure 6, referring to the neural efficiency hypothesis, raises concerns. Efficient visual information processing occurs throughout the visual cortex, starting from V1. Thus, it appears somewhat selective to apply the neural efficiency hypothesis to MT+ in this context.

Transparency Issues:
(1) Don't think it's acceptable to make the claim that "All data needed to evaluate the conclusions in the paper are present in the paper and/or the Supplementary information". It is the results or visualizations of data analysis, rather than the raw data themselves, that are presented in the paper/supp info.

(2) No GitHub link has been provided in the manuscript to access the source data, which limits the reproducibility and transparency of the study.

Minor:
"Locates" should be replaced with "located" throughout the paper. For example: "To investigate this issue, this study selects the human MT complex (hMT+), a region located at the occipito-temporal border, which represents multiple sensory flows, as the target brain area."

Use "hMT+" instead of "MT+" to be consistent with the term in the literature.

"Green circle" in Figure 1 should be corrected to match its actual color.

The abbreviation for the Wechsler Adult Intelligence Scale should be "WAIS," not "WASI."

https://doi.org/10.7554/eLife.97545.1.sa0

Author response:

Thanks for the eLife assessment

> *"This study employed a comprehensive approach to examining how the MT+ region integrates into a complex cognition system in mediating human visuo-spatial intelligence. While the findings are useful, the experimental evidence is incomplete and the study design, hypothesis, analyses, writing, and presentation need to be improved." We plan to revise the manuscript according to the comments of Public Reviews.*

We are grateful for the excellent and very helpful comments, and now we address provisional author responses.

> ***Reviewer #1 (Public Review):***
>
> *Summary:*
>
> *The study of human intelligence has been the focus of cognitive neuroscience research, and finding some objective behavioral or neural indicators of intelligence has been an ongoing problem for scientists for many years. Melnick et al, 2013 found for the first time that the phenomenon of spatial suppression in motion perception predicts an individual's IQ score. This is because IQ is likely associated with the ability to suppress irrelevant information. In this study, a high-resolution MRS approach was used to test this theory. In this paper, the phenomenon of spatial suppression in motion perception was found to be correlated with the visuo-spatial subtest of gF, while both variables were also correlated with the GABA concentration of MT+ in the human brain. In addition, there was no significant relationship with the excitatory transmitter Glu. At the same time, SI was also associated with MT+ and several frontal cortex FCs.*
>
> *Strengths:*
>
> *(1) 7T high-resolution MRS is used.*
>
> *(2) This study combines the behavioral tests, MRS, and fMRI.*
>
> *Weaknesses:*
>
> *(1) In the intro, it seems to me that the multiple-demand (MD) regions are the key in this study. However, I didn't see any results associated with the MD regions. Did I miss something??*

Thank reviewer for pointing this out. After careful consideration, we agree with your point of view. According to the results of Melnick 2013, the motion surround suppression (SI) and the time thresholds of small and large gratings representing hMT+ functionality are correlated with Verbal Comprehension, Perceptual Reasoning, Working Memory, and Processing Speed Indicators, with correlation coefficients of 0.69, 0.47, 0.49, and 0.50, respectively. This suggests that hMT+ does have the potential to become the core of MD system. However, due to our results only delving into "the GABA-ergic inhibition in human MT predicts visuo-spatial intelligence mediated by reverberation with frontal cortex", it is not yet sufficient to prove that hMT+is the core node of the MD system, we will adjust the explanatory logic of the article, that is, emphasizing the de-redundancy of hMT+ in visual-spatial intelligence and the improvement of information processing efficiency, while weakening the significance of hMT+ in MD systems.

> *(2) How was the sample size determined? Is it sufficient??*

Thank reviewer for pointing this out. We use G*power to determine our sample size. In the study by Melnick (2013), they reported a medium effect between SI and Perception Reasoning sub-ability (r=0.47). Here we use this r value as the correlation coefficient (ρ H1), setting the power at the commonly used threshold of 0.8 and the alpha error probability at 0.05. The required sample size is calculated to be 26. This ensures that our study has adequate power to yield valid statistical results. Furthermore, compared to earlier within-subject studies like Schallmo et al.'s 2018 research, which used 22 datasets to examine GABA levels in MT+ and the early visual cortex (EVC), our study includes a more extensive dataset.

> *(3) In Schallmo elife 2018, there was no correlation between GABA concentration and SI. How can we justify the different results different here?*

Thank reviewer for pointing this out. There are several differences between us:

a. While the earlier study by Schallmo et al. (2018) employed 3T MRS, we utilize 7T MRS, enhancing our ability to detect and measure GABA with greater accuracy.

b. Schallmo elife 2018 choose to use the bilateral hMT+ as the MRS measurement region while we use the left hMT+. The reason why we focus on left hMT+ are describe in reviewer 1. (6). Briefly, use of left MT/V5 as a target was motivated by studies demonstrating that left MT/V5 TMS is more effective at causing perceptual effects (Tadin et al., 2011).

c. The resolution of MRS sequence in Schallmo elife 2018 is 3 cm isotropic voxel, while we apply 2 cm isotropic voxel. This helps us more precisely locate hMT+ and exclude more white matter signal.

> *(4) Basically this study contains the data of SI, BDT, GABA in MT+ and V1, Glu in MT+ and V1-all 6 measurements. There should be 6x5/2 = 15 pairwise correlations. However, not all of these results are included in Figure 1 and supplementary 1-3. I understand that it is not necessary to include all figures. But I suggest reporting all values in one Table.*

We thank the reviewer for the good suggestion, we are planning to make a correlation matrix to reporting all values.

> *(5) In Melnick (2013), the IQ scores were measured by the full set of WAIS-III, including all subtests. However, this study only used the visual spatial domain of gF. I wonder why only the visuo-spatial subtest was used not the full WAIS-III?*

We thank the reviewer for pointing this out. The decision was informed by Melnick's findings which indicated high correlations between Surround suppression (SI) and the Verbal Comprehension, Perceptual Reasoning, Working Memory, and Processing Speed Indexes, with correlation coefficients of 0.69, 0.47, 0.49, and 0.50, respectively. It is well-established that the hMT+ region of the brain is a sensory cortex involved in visual perception processing (3D perception). Furthermore, motion surround suppression (SI), a specific function of hMT+, aligns closely with this region's activities. Given this context, the Perception Reasoning sub-ability was deemed to have the clearest mechanism for further exploration. Consequently, we selected the most representative subtest of Perception Reasoning—the Block Design Test—which primarily assesses 3D visual intelligence.

> *(6) In the functional connectivity part, there is no explanation as to why only the left MT+ was set to the seed region. What is the problem with the right MT+?*

We thank the reviewer for pointing this out. The main reason is that our MRS ROI is the left hMT+, we would like to make different models' ROI consistent to each other. Use of left MT/V5 as a target was motivated by studies demonstrating that left MT/V5 TMS is more effective at causing perceptual effects (Tadin et al., 2011). In addition, we will check the results of our localizer to confirm whether similar findings are consistently replicated.

> *(7) In Melnick (2013), the authors also reported the correlation between IQ and absolute duration thresholds of small and large stimuli. Please include these analyses as well.*

We thank the reviewer for the good advice. Containing such result do help researchers compare the result between Melnick and us. We are planning to make such picture in the revised version.

> ***Reviewer #2 (Public Review):***
>
> *Summary:*
>
> *Recent studies have identified specific regions within the occipito-temporal cortex as part of a broader fronto-parietal, domain-general, or "multiple-demand" (MD) network that mediates fluid intelligence (gF). According to the abstract, the authors aim to explore the mechanistic roles of these occipito-temporal regions by examining GABA/glutamate concentrations. However, the introduction presents a different rationale: investigating whether area MT+ specifically, could be a core component of the MD network.*
>
> *Strengths:*
>
> *The authors provide evidence that GABA concentrations in MT+ and its functional connectivity with frontal areas significantly correlate with visuo-spatial intelligence performance. Additionally, serial mediation analysis suggests that inhibitory mechanisms in MT+ contribute to individual differences in a specific subtest of the Wechsler Adult Intelligence Scale, which assesses visuo-spatial aspects of gF.*
>
> *Weaknesses:*
>
> *(1) While the findings are compelling and the analyses robust, the study's rationale and interpretations need strengthening. For instance, Assem et al. (2020) have previously defined the core and extended MD networks, identifying the occipito-temporal regions as TE1m and TE1p, which are located more rostrally than MT+. Area MT+ might overlap with brain regions identified previously in Fedorenko et al., 2013, however the authors attribute these activations to attentional enhancement of visual representations in the more difficult conditions of their tasks. For the aforementioned reasons, It is unclear why*

> *the authors chose MT+ as their focus. A stronger rationale for this selection is necessary and how it fits with the core/extended MD networks.*

We really appreciate reviewer's opinions. The reason why we focus on hMT+ is following: According to the results of Melnick 2013, the motion surround suppression (SI) and the time thresholds of small and large gratings representing hMT+ functionality are correlated with Verbal Comprehension, Perceptual Reasoning, Working Memory, and Processing Speed Indicators, with high correlation coefficients of 0.69, 0.47, 0.49, and 0.50, respectively. In addition, Fedorenko et al. 2013, the averaged MD activity region appears to overlap with hMT+. Based on these findings, we assume that hMT+ does have the potential to become the core of MD system.

> *(2) Moreover, although the study links MT+ inhibitory mechanisms to a visuo-spatial component of gF, this evidence alone may not suffice to position MT+ as a new core of the MD network. The MD network's definition typically encompasses a range of cognitive domains, including working memory, mathematics, language, and relational reasoning. Therefore, the claim that MT+ represents a new core of MD needs to be supported by more comprehensive evidence.*

Thank reviewer for pointing this out. After careful consideration, we agree with your point of view. Due to our results only delving into visuo-spatial intelligence, it is not yet sufficient to prove that hMT is the core node of the MD system. We will adjust the explanatory logic of the article, that is, emphasizing the de-redundancy of hMT+in visual-spatial intelligence and the improvement of information processing efficiency, while weakening the significance of hMT+ in MD systems.

> ***Reviewer #3 (Public Review):***
>
> *Summary:*
>
> *This manuscript aims to understand the role of GABA-ergic inhibition in the human MT+ region in predicting visuo-spatial intelligence through a combination of behavioral measures, fMRI (for functional connectivity measurement), and MRS (for GABA/glutamate concentration measurement). While this is a commendable goal, it becomes apparent that the authors lack fundamental understanding of vision, intelligence, or the relevant literature. As a result, the execution of the research is less coherent, dampening the enthusiasm of the review.*
>
> *Strengths:*
>
> *(1) Comprehensive Approach: The study adopts a multi-level approach, i.e., neurochemical analysis of GABA levels, functional connectivity, and behavioral measures to provide a holistic understanding of the relationship between GABA-ergic inhibition and visuo-spatial intelligence.*
>
> *(2) Sophisticated Techniques: The use of ultra-high field magnetic resonance spectroscopy (MRS) technology for measuring GABA and glutamate concentrations in the MT+ region is a recent development.*
>
> *Weaknesses:*
>
> *Study Design and Hypothesis*
>
> *(1) The central hypothesis of the manuscript posits that "3D visuo-spatial intelligence (the performance of BDT) might be predicted by the inhibitory and/or excitation mechanisms in MT+ and the integrative functions connecting MT+ with the frontal cortex." However, several issues arise:*

> *(1.1) The Suppression Index depicted in Figure 1a, labeled as the "behavior circle," appears irrelevant to the central hypothesis.*

We thank the reviewer for pointing this out. In our study, the inhibitory mechanisms in hMT+ are conceptualized through two models: the neurotransmitter model and the behavior model. The Suppression Index is essential for elucidating the local inhibitory mechanisms within behavior model. However, we acknowledge that our initial presentation in the introduction may not have clearly articulated our hypothesis, potentially leading to misunderstandings. We plan to revise the introduction to better clarify these connections and ensure the relevance of the Suppression Index is comprehensively understood.

> *(1.2) The construct of 3D visuo-spatial intelligence, operationalized as the performance in the Block Design task, is inconsistently treated as another behavioral task throughout the manuscript, leading to confusion.*

We thank the reviewer for pointing this out. We acknowledge that our manuscript may have inconsistently presented this construct across different sections, causing confusion. To address this, we plan to ensure a consistent description of 3D visuo-spatial intelligence in both the introduction and the discussion sections. But we would like to maintain 'Block Design task score' within the results section to help readers clarify which subtest we use.

> *(1.3) The schematics in Figure 1a and Figure 6 appear too high-level to be falsifiable. It is suggested that the authors formulate specific and testable hypotheses and preregister them before data collection.*

We thank the reviewer for pointing this out. We are planning to revise the Figure 1a and make it less abstract and more logical. For Figure 6, the schematic represents our theoretical framework of how hMT+ works in the 3D viso-spatial intelligence, we believe the elements within this framework are grounded in related theories and supported by evidence discussed in our results and discussions section, making them specific and testable.

> *(2) Central to the hypothesis and design of the manuscript is a misinterpretation of a prior study by Melnick et al. (2013). While the original study identified a strong correlation between WAIS (IQ) and the Suppression Index (SI), the current manuscript erroneously asserts a specific relationship between the block design test (from WAIS) and SI. It should be noted that in the original paper, WAIS comprises Similarities, Vocabulary, Block design, and Matrix reasoning tests in Study 1, while the complete WAIS is used in Study 2. Did the authors conduct other WAIS subtests other than the block design task?*

Thanks for pointing this out. Reviewer #1 also asked this question, we copy the answers in here “The decision was informed by Melnick’s findings which indicated high correlations between Surround suppression (SI) and the Verbal Comprehension, Perceptual Reasoning, Working Memory, and Processing Speed Indexes, with correlation coefficients of 0.69, 0.47, 0.49, and 0.50, respectively. It is well-established that the hMT+ region of the brain is a sensory cortex involved in visual perception processing (3D perception). Furthermore, motion surround suppression (SI), a specific function of hMT+, aligns closely with this region's activities. Given this context, the Perception Reasoning sub-ability was deemed to have the clearest mechanism for further exploration. Consequently, we selected the most representative subtest of Perception Reasoning—the Block Design Test—which primarily assesses 3D visual intelligence.”

> *(3) Additionally, there are numerous misleading references and unsubstantiated claims throughout the manuscript. As an example of misleading reference, "the human MT ... a*

> *key region in the multiple representations of sensory flows (including optic, tactile, and auditory flows) (Bedny et al., 2010; Ricciardi et al., 2007); this ideally suits it to be a new MD core." The two references in this sentence are claims about plasticity in the congenitally blind with sensory deprivation from birth, which is not really relevant to the proposal that hMT+ is a new MD core in healthy volunteers.*

Thanks for pointing this out. We have carefully read the corresponding references and considered the corresponding theories and agree with these comments. Due to our results only delving into “the GABA-ergic inhibition in human MT predicts visuo-spatial intelligence mediated by reverberation with frontal cortex”, it is not yet sufficient to prove that hMT+ is the core node of the MD system, we will adjust the explanatory logic of the article, that is, emphasizing the de redundancy of hMT+in visual-spatial intelligence and the improvement of information processing efficiency, while weakening the significance of hMT+ in MD systems. In addition, regarding the potential central role of hMT+ in the MD system, we agree with your view that research on hMT+ as a multisensory integration hub mainly focuses on developmental processes. Meanwhile, in adults, the MST region of hMT+ is considered a multisensory integration area for visual and vestibular inputs, which potentially supports the role of hMT+ in multitasking multisensory systems (Gu et al., J. Neurosci, 26(1), 73–85, 2006; Fetsch et al., Nat. Neurosci, 15, 146–154, 2012.). Further research could explore how other intelligence sub-ability such as working memory and language comprehension are facilitated by hMT+'s features.

> *Another example of unsubstantiated claim: the rationale for selecting V1 as the control region is based on the assertion that "it mediates the 2D rather than 3D visual domain (Born & Bradley, 2005)". That's not the point made in the Born & Bradley (2005) paper on MT. It's crucial to note that V1 is where the initial binocular convergence occurs in cortex, i.e., inputs from both the right and left eyes to generate a perception of depth.*

Thank you for pointing this out. We acknowledge the inappropriate citation of "Born & Bradley, 2005," which focuses solely on the structure and function of the visual area MT. However, we believe that choosing hMT+ as the domain for 3D visual analysis and V1 as the control region is justified. Cumming and DeAngelis (Annu Rev Neurosci, 24:203–238.2001) state that binocular disparity provides the visual system with information about the three-dimensional layout of the environment, and the link between perception and neuronal activity is stronger in the extrastriate cortex (especially MT) than in the primary visual cortex(V1). This supports our choice and emphasizes the relevance of MT+ in our study. We will revise our reference in the revised version.

> *Results & Discussion*
>
> *(1) The missing correlation between SI and BDT is crucial to the rest of the analysis. The authors should discuss whether they replicated the pattern of results from Melnick et al. (2013) despite using only one WAIS subtest.*

We thank for reviewer’s suggestion. Now the correlation result is placed in the supplemental material, we will put it back to the main text.

> *(2) ROIs: can the authors clarify if the results are based on bilateral MT+/V1 or just those in the left hemisphere? Can the authors plot the MRS scan area in V1? I would be surprised if it's precise to V1 and doesn't spread to V2/3 (which is fine to report as early visual cortex).*

We thank for reviewer’s suggestion. We plan to draw the V1 ROI MRS scanning area and use the visual template to check if the scanning area contains V2/3. If it does, we will refer to it as

the early visual cortex rather than specifically V1 in our reporting.

> *(3) Did the authors examine V1 FC with either the frontal regions and/or whole brain, as a control analysis? If not, can the author justify why V1 serves as the control region only in the MRS but not in FC (Figure 4) or the mediation analysis (Figure 5)? That seems a little odd given that control analyses are needed to establish the specificity of the claim to MT+*

We thank for reviewer's suggestion. We plan to do the V1 FC-behavior connection as control analysis. For mediation analysis, since V1 GABA/Glu has no correlation with BDT score, it is not sufficient to apply mediation analysis.

> *(4) It is not clear how to interpret the similarity or difference between panels a and b in Figure 4.*

We thank reviewer for pointing this out. We plan to further interpret the difference between a and b in the revised version. Panels a represents BDT score correlated hMT+-region FC, which is obviously involved in frontal cortex. While panels b represents SI correlated hMT+-region FC, which shows relatively less regions. The overlap region is what we are interested in and explain how local inhibitory mechanisms works in the 3D viso-spatial intelligence. In addition, we would like to revise Figure 4 and point out the overlap region.

> *(5) SI is not relevant to the authors' priori hypothesis, but is included in several mediation analyses. Can the authors do model comparisons between the ones in Figure 5c, d, and Figure S6? In other words, is SI necessary in the mediation model? There seem discrepancies between the necessity of SI in Figures 5c/S6 vs. Figure 5d.*

We thank the reviewer for highlighting this point. The relationship between the Suppression Index (SI) and our a priori hypotheses is elaborated in the response to reviewer 3, section (1). SI plays a crucial role in explicating how local inhibitory mechanisms function within the context of the 3D visuo-spatial task. Additionally, Figure 5c illustrates the interaction between the frontal cortex and hMT+, showing how the effects from the frontal cortex (BA46) on the Block Design Task are fully mediated by SI. This further underscores the significance of SI in our model.

> *(6) The sudden appearance of "efficient information" in Figure 6, referring to the neural efficiency hypothesis, raises concerns. Efficient visual information processing occurs throughout the visual cortex, starting from V1. Thus, it appears somewhat selective to apply the neural efficiency hypothesis to MT+ in this context.*

We thank the reviewer for highlighting this point. There is no doubt that V1 involved in efficient visual information processing. However, in our result, the V1 GABA has no significant correlation between BDT score, suggesting that the V1 efficient processing might not sufficiently account for the individual differences in 3D viso-spatial intelligence. Additionally, we will clarify our use of the neural efficiency hypothesis by incorporating it into the introduction of our paper to better frame our argument.

> *Transparency Issues:*
>
> *(1) Don't think it's acceptable to make the claim that "All data needed to evaluate the conclusions in the paper are present in the paper and/or the Supplementary information". It is the results or visualizations of data analysis, rather than the raw data themselves, that are presented in the paper/supp info.*

We thank reviewer for pointing this out. We realized that such expression will lead to confusion. We will delete this expression.

> *(2) No GitHub link has been provided in the manuscript to access the source data, which limits the reproducibility and transparency of the study.*

We thank reviewer for pointing this out. We will attach the GitHub link in the revised version.

> *Minor:*
>
> *"Locates" should be replaced with "located" throughout the paper. For example: "To investigate this issue, this study selects the human MT complex (hMT+), a region located at the occipito-temporal border, which represents multiple sensory flows, as the target brain area."*

We thank reviewer for pointing this out. We will revise it.

> *Use "hMT+" instead of "MT+" to be consistent with the term in the literature.*

We thank reviewer for pointing this out. We agree to use hMT+ in the literature.

> *"Green circle" in Figure 1 should be corrected to match its actual color.*

We thank reviewer for pointing this out. We will revise it.

> *The abbreviation for the Wechsler Adult Intelligence Scale should be "WAIS," not "WASI."*

We thank reviewer for pointing this out. We will revise it.