Deactivation of the default mode network is associated with resting-state glutamate and GABA

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Introduction The default mode network (DMN) deactivation observed with BOLD fMRI is thought to be associated with suppression of spontaneous brain activities and reallocation of resources to ongoing, attention-demanding tasks [1]. Stronger DMN deactivation in a working memory (WM) task predicts better performance in healthy subjects [2]. Conversely, failures of DMN deactivation have been observed in several mental disorders [3,4]. These findings indicate the importance of DMN deactivation contributing to both normal cognitive functions and psychiatric disorders. However, the underlying neurochemical mechanism of DMN deactivation remains largely unknown. The coordination between glutamate (Glu) and GABA transmissions is believed to have a direct impact on BOLD contrast [5,6]. The current study aimed to examine the relationship between DMN deactivation induced by a WM task and the endogenous concentrations of Glu and GABA in the posterior cingulate/precuneus (PCC/PCu) region, a hub of the DMN.

Methods Twenty-four healthy subjects (age: 34.4 ± 8.6; 10 females) participated in the study. Participants were screened for drugs of abuse (urine toxicology) including benzodiazepines on the day of scanning. MRS and fMRI scans were performed on a Siemens 3T Trio scanner using a 12-channel coil. A 2.4×3.2×3.6 cm^3 voxel of interest (VOI) was placed at the PCC/PCu (Fig. 1a), and a control region was placed in the primary visual cortex. A MEGA-PRESS sequence was used to measure GABA (TE/TR = 68/5000 ms; 96 averages) and a PRESS sequence for Glu (TE/TR = 30/3000 ms; 128 averages). All MRS data were quantified using LCModel. In the fMRI session, participants performed a 14-min block-design n-back WM task, including four conditions: 0-back (0b), 1-back (1b), 2-back (2b), and 3-back (3b). A single-shot gradient EPI sequence was used to acquire BOLD images (TR/TE = 2000/27 ms; FA=78^0; slice thickness = 4mm; 39 slices; FOV = 220×220 mm^2 with in-plane resolution of 3.44×3.44 mm^2). Preprocessing steps for fMRI data included slice-timing correction, head motion correction, spatial smoothing with a 6-mm Gaussian kernel, and quadratic detrending. General linear modeling was used to assess WM effect on brain activity. A region of interest (ROI) in the PCC/PCu area was selected based on the WM main effect at the significance level of $p < 0.01$ (corrected for multiple comparisons). Relationships between deactivation and neurotransmitters were examined with multiple regression analyses. Age and VOI gray matter volume (GMV) were included in the model because of their potential influences.

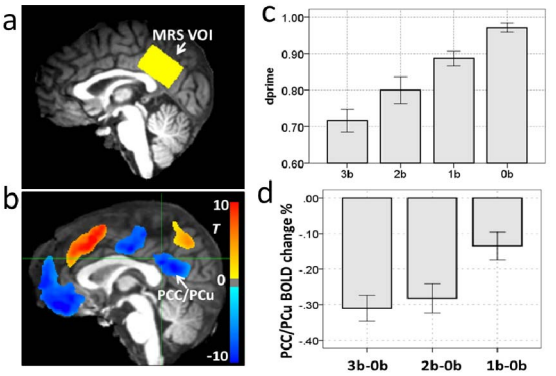

Fig.1 a) MRS VOI. b) WM induced brain activity. c) WM performance. d) ROI BOLD signal change.

Table 1 Coefficients in regression models

WM		B(Std.Err)	B'	t	Sig.
1b	Age	.018(.004)	.815	4.612	.0002
	GMV	-.918(.775)	-.216	-1.185	.251
	Glu	.261(.076)	.640	3.446	.003
	GABA	-.121(.060)	-.321	-2.003	.060
2b	Age	.016(.004)	.674	3.583	.002
	GMV	-1.262(.870)	-.282	-1.451	.163
	Glu	.297(.085)	.690	3.489	.002
	GABA	-.190(.068)	-.480	-2.812	.011
3b	Age	.014(.004)	.670	3.947	.001
	GMV	-.702(.694)	-.178	-1.012	.324
	Glu	.275(.068)	.724	4.053	.0007
	GABA	-.216(.054)	-.617	-4.004	.0008

Dependent Variable: PCC/PCu deactivation. Predictors: (Constant), age, GM, Glu, GABA. B (Std.Err): Unstandardized coefficient (Standard Error). B' : Standardized coefficient.

Result Glu and GABA concentrations in the PCC/PCu VOI were 7.46 ± .56 mM, and 1.82 ± .20 mM, respectively. The task-induced deactivation regions were well-overlapped with the DMN, including the PCC/PCu, medial prefrontal cortex, hippocampus, parahippocampal gyrus, superior temporal gyrus, and transverse temporal gyrus (Fig.1b). When the WM load increased, the task performance (dprime) decreased (Fig.1c) while the DMN deactivation was enhanced (Fig.1d). The BOLD signal changes within the PCC/PCu ROI at 1b, 2b and 3b were predicted by age, GMV and the Glu and GABA concentrations in the PCC/PCu VOI (Table 1). Age and Glu were positively correlated with BOLD signal changes while GABA showed negative association (Fig. 2). Regional Glu and GABA concentrations (5.44 ± .72 and 1.98 ± .22 mM) of the control region did not showed significant association with PCC/PCu BOLD signal changes in the same analysis.

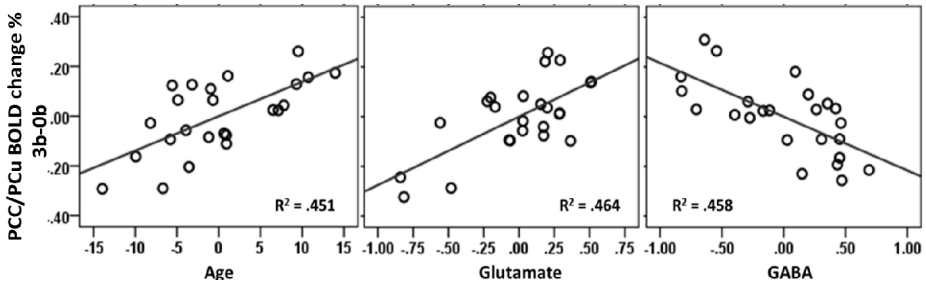

Fig.2 Partial plots for 3b. Patterns of these associations are similar for 1b and 2b.

Discussion The present study demonstrates significant associations between neurotransmitters and the DMN deactivation probed by a WM task. The major excitatory neurotransmitter, Glu, prevents BOLD signal from deactivation while GABA, the major inhibitory neurotransmitter, exerts opposite effects. The balance between excitation and inhibition of the neural system is important for brain functioning and the altered cellular excitation/inhibition balance has been suggested to be implicated in psychiatric disorders such as autism and schizophrenia [7]. These neurochemical characteristics of DMN deactivation reported in the current study may provide novel insights into DMN's functions in healthy individuals and dysfunction in brain disorders.

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Reference

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