Unbalance Between Working Memory Task-Activation and Task-Deactivation Networks in Epilepsy: Simultaneous EEG-fMRI Study

Yun Qin (✉ qyuner@163.com)

University of Electronic Science and Technology of China <https://orcid.org/0000-0002-8106-6137>

Sisi Jiang

University of Electronic Science and Technology of China

Lili Yang

University of Electronic Science and Technology of China

Dezhong Yao

University of Electronic Science and Technology of China

Cheng Luo

University of Electronic Science and Technology of China

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Abstract

Working memory (WM) is one cognitive function, involving emergent properties of theta oscillation and large-scale network interactions. The synchronization of WM task-related networks in brain enhanced working memory performance. However, how these networks regulated WM processing was not well known, and the alteration of the interaction among these networks may play an important role in the patients with cognitive dysfunction. In this study, we used simultaneous EEG-fMRI to examine the features of theta oscillation and the functional interactions among activation/deactivation networks during n-back WM task in patients with idiopathic generalized epilepsy (IGE). The results showed that there was more enhancement of frontal theta power along with WM load increasing in IGE, and the theta power was positively correlated with the accuracy of the WM tasks. Moreover, fMRI activations/deactivations correlated with n-back tasks were estimated, and we found that IGE group had increased and widespread activations in high-load WM task, including frontoparietal activation network, and the task-related deactivation areas, such as the default mode network, primary visual and auditory networks. In addition, the result of network connectivity demonstrated decreased counteraction between activation network and deactivation network, and the counteraction was correlated with the higher theta power in IGE. These results indicated the important role of the interactions between activation and deactivation networks during WM process, and the unbalance among them may imply the pathophysiological mechanism of cognitive dysfunction in generalized epilepsy.

1 Introduction

Neural oscillations modulated the local and inter-regional activity, and contributed to the information processing and cognitive performance (Buzsaki & Draguhn, 2004; Klimesch, 1999). Cognitive function such as working memory (WM) comprised emergent properties of neural oscillations and large-scale network interactions (Sreenivasan et al., 2014). Previous studies have demonstrated that the reactivity of theta bands (4–8 Hz) to various memory paradigms illuminated the cortico-cortical interactions needed in case of increasing memory load (Johnson et al., 2018; Zakrzewska & Brzezicka, 2014). Strengthened theta power and widespread theta synchrony based on EEG recording has been shown underlying enhanced memory load, as well as the performance of the WM task (Hsieh & Ranganath, 2014; Toth et al., 2012). While in patients with cognitive decline, impaired theta oscillation and brain connectivity was exhibited during WM processing (Missonnier et al., 2006; Sarnthein et al., 2005). Theta response over frontal regions increased network efficiency, primarily reflecting the activation of neural networks involved in the allocation of attention, attention control, thus played an important role in directing local activity and long-range interactions during information processing in WM (Deiber et al., 2007; Rutishauser et al., 2010).

Frontal and parietal brain regions supported WM processing (Cohen et al., 1997; Todd & Marois, 2004), and the regulation among frontoparietal and frontotemporal networks modulated the spatiotemporal dynamics and enhanced working memory performance (Klingberg et al., 1997; Violante et al., 2017). Therefore, frontoparietal network was widely thought to be the task-activation network in WM. In addition,

the default mode network (DMN) arising from the resting-state fMRI, which showed great deactivation in WM, also demonstrated interaction with the WM activation network, and facilitated the working memory performance (Koshino et al., 2014; Xin & Lei, 2015). Therefore, it was suggested the existence of modulation between task-activation and task-deactivation brain networks played an important role on WM processing (Koshino et al., 2014; Newton et al., 2011). However, how the connectivity between task-activation and deactivation networks modulated the WM processing, and the relationship between these networks and theta oscillation was still less known.

The impairment of WM has been reported in local epilepsy, such as temporal lobe epilepsy and frontal lobe epilepsy (Santana et al., 2006; Stretton et al., 2012), as well as in generalized epilepsy (Myatchin et al., 2009; Swartz et al., 1996), which was one common epileptic subtype involving distributed altered activity and network connectivity in brain. The altered representations of functional networks relative to WM in generalized epilepsy was not yet to be fully investigated. In fact, the dysfunction of the frontal and parietal regions was a key element contributing to discharge generation and propagation (Bai et al., 2010; Lee et al., 2014; Vaudano et al., 2009), while these regions were also involved in the working memory networks. Moreover, aberrant activity and functional connectivity in DMN, which was task-deactivation network in WM, played an important role in brain dysfunction and discharge activity in epilepsy (Gotman et al., 2005; Luo et al., 2011; Qin et al., 2019). Meanwhile, diffuse and hypersynchronous theta oscillation was also found in epileptic circuits (Clemens, 2004).

Therefore, probing how the functional networks and theta oscillation altered in WM processing and the relationship among them may be helpful for understanding the cognition dysfunction in epilepsy brain.

In this study, we used simultaneous EEG and fMRI to examine the features of neural oscillation and the functional connectivity during n-back WM task in patients with idiopathic generalized epilepsy (IGE). Theta power in frontal electrodes was calculated, and fMRI activations/deactivations correlated with n-back tasks were estimated. Moreover, functional connectivity dependent on the WM task among activation and deactivation networks was examined using psychophysiological interaction (PPI) (Friston et al., 1997), which aimed to detect the coupling of one region to another with the modulation of other experimental or intrinsic factors. Finally, the relationship between theta features and WM-related functional connectivity in epilepsy was investigated.

2 Materials And Methods

Participants

Thirty-four patients with IGE were recruited in this study (18 females; mean age: 27 years). Diagnosis and classification was made by neurologists in accordance with the International League Against Epilepsy (ILAE) guidelines (Fisher et al., 2017; Scheffer et al., 2017). The patients in this study were mostly characterized with generalized tonic-clonic seizures. Routine CT and MRI examinations were conducted and no structural abnormality was found in all epilepsy patients. Thirty-two healthy controls (21 females; mean age: 23.3 years) with no history of psychiatric or neurologic disorders participated in the study.

Summary demographic of patients and healthy controls was shown in Table 1. Written informed consent according to the Declaration of Helsinki was obtained from all participants. This study was approved by the Ethics Committee of the University of Electronic Science and Technology of China (UESTC).

Table 1
Summary demographic of patients and healthy controls

	HC		Patients		χ^2 / t-test	
	<i>n</i> = 33		<i>n</i> = 34		<i>p</i> value	
Gender (Male/Female)	12/21		16/18		0.375	
Seizure type	-		IGE		-	
	Mean	Std	Mean	Std		
Age(year)	23.3	2.4	27	9.2	0.053	
Seizure duration	-	-	5.06	5.56	-	-
Age at seizure onset	-	-	22.3	10.4	-	-

Stimuli and task

Participants performed a visual N-back WM task with two memory loads, i.e., 1-back and 2-back. Here, we used a block-design paradigm to separate the task effects. Instructions and a short practice were given outside the scanner before scanning. There were also verbally instructions at the beginning of each run. Two runs were conducted for each participant. In each block, lists of stimuli with three kinds of shapes (square, circle, triangle) were presented in a pseudorandom order. Each run consisted of a resting period of 10s and a screen tip of 4s, immediately followed by six blocks, with an inter-block interval of 14s. Each 1-back block lasted 44s, within which 22 stimuli were presented one at a time (2500ms of exposure time for each stimulus) with an inter-stimuli interval of 1500ms. Each 2-back block lasted 48s with 24 stimuli presented, with 2500ms of exposure time for each stimulus and 1500ms of inter-stimuli interval. Participants were instructed to pay attention to a sequence of visual stimuli, and press one pre-defined button, as far as possible, each time the stimulus was the same as one or two trials earlier according to 1-back or 2-back instructions, while press the other button when the stimulus was different. In the resting periods, participants were told to keep still and pay attention to a fixation point without any response. The experiment procedure was shown in Fig. 1.

Simultaneous EEG-fMRI acquisition

FMRI data in the condition of WM tasks were acquired using a 3T MRI scanner (Discovery MR750, GE) with an eight channel-phased array head coil, and a gradient-echo planar imaging sequences (FOV = 24 × 24 cm², FA = 90°, TR / TE = 2000 ms / 30 ms, matrix = 64 × 64, slice thickness/gap = 4 mm/0.4 mm).

High-resolution T1-weighted images were also acquired using a 3-D fast spoiled gradient echo (T1-3D FSPGR) sequence (FOV = $25.6 \times 25.6 \text{ cm}^2$, FA = 9° , matrix = 256×256 , TR / TE = 5.936 ms / 1.956 ms, slice thickness = 1 mm, no gap, 152 slices).

Simultaneous EEG in the condition of WM tasks were recorded by means of a MR compatible EEG cap (64-channel, Neuroscan, Charlotte, NC). Electrodes were placed according to the 10–20 standard system. Before recording, Fcz was the recording reference and electrode impedances were lowered to below 10k Ω . The amplifier was settled outside the scanning room and the sampling rate was set at 5000 Hz. Synchronization between MR scanner's internal clock and the EEG recording facilitated the artifacts removal in EEG preprocessing.

EEG-fMRI data preprocessing

fMRI data were preprocessed using SPM12 (<http://www.fil.ion.ucl.ac.uk/spm/>). The first five volumes were discarded from all fMRI scans for the magnetization equilibrium. The remaining volumes were slice-timing corrected and spatially realigned. Individual T1 images were coregistered to the functional images, and segmented and normalized to the Montreal Neurologic Institute (MNI) space. All subjects have < 1 mm for head movement and 1° for head rotation during MRI scanning, and there was no head motion difference between the two groups. Then, the functional images were spatially normalized based on T1 transformation matrix, resampled to $3 \times 3 \times 3 \text{ mm}^3$ voxels, and spatially smoothed using a 6 mm full-width half maximum (FWHM) Gaussian kernel. Nuisance signals (12 motion parameters, linear drift signal, as well as mean white matter and cerebrospinal fluid signals) were regressed out for the fMRI data.

Curry 7 software (Compumedics Neuroscan) was used to correct MR gradient artifacts and the ballistocardiogram (BCG) artifacts. The gradient artifacts were removed via template subtraction method using the triggers delivered from the MR scanner (Allen et al., 2000). Band-pass filtering (0.5-45Hz) was performed following by the down-sampling to 250 Hz. Then, BCG artifacts were removed using the optimal basis set (OBS) based method according to ECG channel (Niazy et al., 2005). Finally, the preprocessed EEG were re-referenced to the neutral infinite reference using Reference electrode standardization technique (REST) (Yao, 2001).

Spectral analysis of frontal theta rhythm

Spectral analysis was conducted to the preprocessed EEG. As theta oscillation was widely considered being related to the WM processing, we focused on the frontal electrodes, i.e., F3 and F4, and extracted the power of theta rhythm (4-8Hz). The averaged theta power spectral density (PSD) in 1-back blocks and 2-back blocks were calculated based on the Welch's averaged periodogram method. Then, we used the repeated measure ANOVAs to detect the group main effect, the task main effect and the interaction effect of theta power in F3 and F4, respectively. In addition, we proposed the normalized theta metric to investigate the effect arising from the increasing WM load. The normalized PSD of frontal theta was obtained using the difference between 2-back and 1-back divided by the PSD of 1-back.

FMRI activation analysis

Whole-brain statistical analysis of fMRI data was performed using the generalized linear model (GLM). For the first-level analysis, task-related fMRI activations and deactivations in single-subject were calculated. The stimuli variations of n-back tasks were convolved with the standard haemodynamic response function and then used as regressors in the GLM. The response during 1-back blocks was subtracted from that during the 2-back blocks. Then, the second-level analysis was conducted using the statistical images resulting from single-subject contrasts to examine the activation effect of 2-back conditions at within-group (one-sample t-test) and between-group (two-sample t-test) level.

PPI analysis

PPI analysis aimed to identify the contribution of one region to another with the modulation of experimental factors. The PPI model included correlation PPI terms, i.e., psychological variates and physiological variates, and modulatory interaction term. In this study, PPI analysis was performed based on the regions which represented significant between-group difference in the WM-related fMRI activation maps. The regions with significant difference ($P < 0.01$) were selected as the regions of interest (ROI, $3 \times 3 \times 3$ voxels), and the mean BOLD signals within the ROIs were extracted for each participant. Then, the connections among these ROIs depending on the 2-back condition was analyzed using PPI model to detect the potential interaction effect between ROIs in the modulation of 2-back task. Here, X_{r1} and Y_{r2} was averaged BOLD signal of the two selected ROIs. We constructed the psychological regressor X_{task} as the stimulus under 2-back conditions. The interaction term X_{int} was the point-by-point

multiplication between the psychological signal and the physiological signal, i.e., $X_{r1_deconv} \cdot X_{task}$,

where the physiological regressor X_{r1_deconv} was the estimate of neural activity derived by deconvolution of HRF from the BOLD time series. Therefore, the significant coupling effect β_{int} between two ROIs was considered to be the task-modulated functional connectivity.

$$Y_{r2} = \beta_0 + \beta_1 X_{r1} + \beta_{task} (X_{task} \cdot HRF) + \beta_{int} (X_{int} \cdot HRF)$$

Statistical Analysis

First, two-sample t-test was conducted to examine the between-group effect of the normalized theta PSD. Then, the frontal theta power, i.e., sum of the F3 and F4 PSD was correlated with the behavior measurement (the response time and accuracy) during WM tasks. As for the fMRI data, the activation effects were obtained based on the two-level analysis. The statistical maps were corrected for multiple comparisons with false discovery rate (FDR) calculation. Moreover, after PPI analysis, the comparison of task-modulated functional connectivity was conducted between groups (two-sample t-test). Finally, the relationship between fMRI features and frontal theta power in the condition of 2-back task in IGE patients was examined. Here the frontal theta power was the averaged theta-PSD in F3 and F4 in this condition.

The activation in ROI and PPI connections between ROIs which was significant altered in IGE group were extracted, and then *pearson* correlation with the theta PSD in 2-back task was performed.

3 Results

Group-level analysis of behavior data

The response time (RT) and accuracy (ACC) in n-back tasks was submitted to a repeated measure ANOVAs and the post-hoc t-tests. In within-group level, IGE group showed increased RT and decreased ACC with the increasing memory load ($P < 0.001$), while there was no significant difference between 1-back and 2-back task in HC. Comparing to HC, IGE group demonstrated significant decrease for ACC in 2-back task, as well as increase for RT in 1-back task ($P < 0.05$). In addition, interaction effect was found for both RT and ACC between the group and WM load ($P < 0.001$ for ACC, and $P = 0.052$ for RT).

Results of frontal theta rhythm

The results showed that there was significant task effect of theta-PSD in both F3 and F4 electrodes ($P < 0.05$). That is, the increasing of working memory load was accompanied with the significant enhancement of frontal theta-PSD. However, no significant group effect and interaction effect was found. In addition, we calculated the normalized theta-PSD metric and conducted two-sample t-test. Comparing to HC, the normalized theta-PSD in IGE was significantly increased in frontal electrodes. Moreover, the sum of the frontal PSD was positively correlated with the ACC in 2-back tasks. The results of the frontal theta power were shown in Fig. 2.

FMRI activations and deactivations related to 2-back task

We calculated the brain activation maps correlated to n-back WM task in epilepsy and HC. The results of comparisons within-group and between-group were shown in Fig. 3. In both HC and IGE group, the task-activations correlated to n-back tasks were dominant in frontoparietal network, while the task-deactivations involved the default mode network (DMN), the primary visual, auditory and motor cortex, as well as the cerebellum. Moreover, more activations in frontoparietal network occurred with the WM load increasing. In the 2-back > 1-back contrast, there were higher and broader activations in frontoparietal areas, as well as a few of increased deactivations in DMN areas, mainly in middle and post cingulate cortex. Here, we defined the frontoparietal regions which represented activations in 2-back task as the working memory network (WMN), including *supp_motor_area* (SMA), *frontal_sup*, *frontal_mid*, *parietal_sup*, and *parietal_inf* areas. Comparing to HC, there were much wider activation areas in both 1-back and 2-back tasks in IGE, while the deactivation areas diminished greatly. With the WM load increasing, widespread enhanced activations were found in IGE comparing to HC, including the areas in WMN, DMN, and occipital / temporal areas ($P < 0.001$, two-sample t-test, Fig. 4 and Table 2). These brain areas which were demonstrated significant alteration in IGE were selected as ROIs for the following PPT analysis.

Table 2
Between group comparisons (IGE-HC) of brain activation maps
correlated with 2back > 1back contrast ($P < 0.001$)

MNI coordinate(mm)					
Brain regions	X	Y	Z	T-value	cluster
Frontal_Sup_L	-3	33	60	4.2712	28
Frontal_Sup_R	27	51	42	4.0451	24
Supp_Motor_Area_L	-2	23	66	3.8675	19
Precuneus_R	6	-51	42	4.3715	45
Cuneus_L	-15	-75	27	4.0585	20
Angular_R	53	-61	30	4.0575	106
Occipital_Mid_R	36	-87	18	4.8453	90
Temporal_Mid_R	51	-61	18	4.1643	67

PPI network results

The directed network among ROIs which was dependent on 2-back tasks was constructed based on PPI analysis. Here, ROIs were selected demonstrating significant alteration of activations/deactivations in IGE (here the threshold was settled as $P < 0.01$). Comparing to HC, decreased positive connectivity was located among the deactivation regions in IGE, including the DMN, occipital and temporal areas. Moreover, IGE showed decreased negative connectivity between frontal WMN areas and the deactivation networks, such as the occipital area and the middle cingulum. The significant group-level connections based on PPI analysis were shown in Fig. 5.

Correlation between theta feature and task-dependent network features

Correlation between theta power and PPI connectivity, as well as the fMRI activations in ROIs depending on 2-back tasks was performed. The result was shown in Fig. 5b. It was found that the fMRI activations in WMN regions, i.e., frontal_sup_medial and SMA, was accompanied with the increased frontal theta power. In addition, the increased negative connectivity between these WMN regions and occipital regions was accompanied with the increased frontal theta power.

4 Discussion

This study investigated the EEG and fMRI representations related to n-back WM task. The enhancement of frontal theta power was accompanied with the increasing of working memory load, as well as the behavior accuracy in IGE. Moreover, fMRI activations were demonstrated in working memory network

during n-back tasks, while IGE group showed more distributed activations in frontal activation network, DMN, and primary visual and auditory network. In addition, the functional connectivity among these regions dependent on the 2-back task was constructed using PPI analysis, and decreased negative connectivity both within the frontal activation network and deactivation network, as well as the decreased positive connectivity between the activation network and deactivation network was found. Finally, the relationship with frontal theta power indicated the unbalance of the anticorrelation between activation and deactivation network disturbed the efficiency of the WM process in IGE.

Theta oscillations were widely found in many cognitive activity, involved in allocation of attention, attention control, directing local and long-range activity during information processing (Missonnier et al., 2006; Ward, 2003). In working memory tasks, the power and connectivity of theta band was enhanced, accompanying with the highly increased synchronization of theta rhythm (Itthipuripat et al., 2013). In the current study, increased theta power in frontal electrodes was demonstrated in 2-back task contrast to 1-back task. The activity of frontal theta during the period of working memory played a positive role with the increasing demand for attention and central execution (Jensen & Tesche, 2002). Moreover, this increase of theta was observed in both epilepsy group and HC group. Although the absolute theta power was much lower in IGE group, the relative increase of theta in 2-back task versus 1-back, i.e., normalized theta power in IGE, was significantly higher than that in HC. These results indicated that the enhancement of theta oscillation was necessary for the increasing WM load, while in IGE, much more efforts may be needed to facilitate the resource allocation and information processing in WM task.

Previous studies showed that theta related network in working memory directed the information flowing from frontal to other brain regions (Honey et al., 2002; Klingberg et al., 2002; Nee & Brown, 2013), and working memory capacity was enhanced by distributed prefrontal activation (Tang et al., 2019). As the current study showed, the fMRI activations correlated to n-back tasks involved distributed frontal and parietal areas, while deactivation in DMN and primary visual/auditory networks was also demonstrated. Moreover, with the increasing WM load, much higher and broader activations in frontoparietal areas were found. That is, increasing resources required in high-level WM task made some areas in deactivation networks such as DMN, converting to activation areas. The results were consistent with the previous common findings (Koshino et al., 2005; Vu et al., 2013). While in epilepsy, abnormal brain activation and connectivity has been demonstrated in patients with focal epilepsy (Lv et al., 2014; Stretton et al., 2012), and higher ERP amplitude was found in idiopathic epilepsy comparing to the control group over frontal and central regions (Myatchin et al., 2009). In the current study, increased activation and the diminished deactivation in IGE implied the abnormality of resource mediation of working memory processing. The decreased deactivation of DMN may be related with the inefficient balance and regulation of the introspective and the exterior input processing in tasks in epilepsy.

This study used PPI model to detect the functional connectivity dependent on the working memory tasks. Anticorrelation between frontoparietal network and default networks supported goal-directed cognition and working memory process (Piccoli et al., 2015; Spreng et al., 2010). This counteraction between activation network and deactivation network may be associated with the top-down processing, serving as

the cortical mediator linking the introspective and the exterior input processing (Xin & Lei, 2015). In the other hand, aberrant functional connectivity in epilepsy has been widely reported in thalamocortical circuit and widespread cortical networks, such as frontal central execution network, sensorimotor network and DMN (Clemens et al., 2013; Jiruska et al., 2013). In this study, decreased negative coupling between frontal activation areas and the deactivation areas was found in epilepsy, which indicated the unbalance between the task-positive network and task-negative network. The decreased positive connectivity within deactivation areas may be also associated with the extending activation and the decreased deactivation, which imply the re-allocation of the WM resource in epilepsy. Moreover, the negative relationship between the disturbed connectivity and frontal theta power also illuminated the role of the counteraction between activation network and deactivation network on the information processing and resource allocation underling enhanced cognition (Solomon et al., 2017). The disrupted anti-correlation and the decreased theta power may be indicators of the abnormal WM function suffering from the long-term epileptic activity.

There are several limitations in this study. First, we performed n-back block WM tasks according to the time of repetition (TR) in fMRI scanning. This block paradigm was unable to refine the specific stages of process, such as the encoding manipulation, active maintenance and retrieval of information. Second, the relationship between local theta oscillation and the functional connectivity was investigated, however, more in-depth exploration about the causality among them and the role in modulating WM processing is needed in the future study. In addition, as the WM tasks represented summarization of the attention, memory and execution function, combing the brain features with the behavior and the clinical evaluations would be helpful for uncovering the impairment of cognitions in epileptic brain.

5 Conclusion

This study investigated the relationship of EEG and fMRI-based activation, as well as the functional connectivity in n-back working memory task. Enhancement of the activations in frontal activation network, DMN, and primary network was found in IGE. In addition, the functional connectivity using PPI analysis demonstrated altered connectivity among the activation and deactivation networks in IGE. Our findings demonstrated the unbalance of the interactions between activation and deactivation networks during working memory process in IGE, and the correlation with the theta power may imply the pathophysiological mechanism of working memory dysfunction in epilepsy.

Declarations

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Author contributions

YQ, CL and DY had made a substantial contribution to the conception and drafting and revising the article; SJ, LY had made a substantial contribution to the analysis and interpretation of the data, and then they gave final approval of the version to be published.

Compliance with ethical standards

Conflicts of Interest

No conflicts of interest to declare.

Ethical approval

All procedures performed in study involving participants were in accordance with the Ethics Committee of the University of Electronic Science and Technology of China in accordance with the Helsinki Declaration.

Informed consent

Informed consent was obtained from all subjects included in the study.

Data availability statements

The data that support the findings of this study are available from the corresponding author upon request.

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Figures

Figure 1

Working memory experimental protocol used in the current study.

Figure 2

a-b The ANOVA results of frontal theta-PSD in F3 and F4 electrodes. The increasing of working memory load was accompanied with the significant enhancement of theta-PSD. **c** The normalized theta-PSD in F3 and F4 electrode. Significant difference was demonstrated between IGE and HC. **d** Positive correlation between frontal theta power and the accuracy index during WM processing.

Figure 3

Brain activation maps correlated to n-back WM task in epilepsy and HC. Widespread activation was found in IGE in different conditions of WM processing.

Figure 4

Between group result (IGE-HC) of the fMRI activation correlated with 2-back>1-back contrast ($P < 0.05$, FDR-corrected).

Figure 5

Group-level results of PPI connections dependent on 2-back WM task. **a** Two sample t-test result of PPI connections between IGE and HC. The red line denoted decreased negative coupling, and the blue line denoted decreased positive coupling in IGE. **b** Correlation between frontal theta-PSD in 2-back WM task and the fMRI activation, as well as the PPI connections.

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