The Effects of Dexamphetamine on the Resting-State Electroencephalogram and Functional Connectivity

Matthew A. Albrecht,^{1,2,3,4,*} Gareth Roberts,^{5,6,7} Greg Price,^{8,9} Joseph Lee,^{9,10}
Rajan Iyyalol,¹⁰ and Mathew T. Martin-Iverson^{4,8}

¹*School of Public Health, Curtin University, Western Australia, Australia*

²*Curtin Health Innovation Research Institute-Biosciences, Curtin University, Perth, Western Australia*

³*School of Medicine, University of Maryland, Maryland Psychiatric Research Center, Maryland*

⁴*Pharmacology, Pharmacy and Anaesthesiology Unit, School of Medicine and Pharmacology, the University of Western Australia, Western Australia, Australia*

⁵*School of Psychology and Exercise Science, Murdoch University, Western Australia, Australia*

⁶*School of Psychology, University of Sydney, Sydney, New South Wales, Australia*

⁷*Centre for Research on Computer Supported Learning and Cognition, University of Sydney, Sydney, New South Wales, Australia*

⁸*Department of Neurophysiology, North Metropolitan Area Mental Health Service, Department of Health, Western Australia*

⁹*Psychiatry and Clinical Neurosciences, School of Medicine and Pharmacology, the University of Western Australia, Western Australia, Australia*

¹⁰*Graylands Hospital, Western Australia, Australia*

Abstract: The catecholamines—dopamine and noradrenaline—play important roles in directing and guiding behavior. Disorders of these systems, particularly within the dopamine system, are associated with several severe and chronically disabling psychiatric and neurological disorders. We used the recently published group independent components analysis (ICA) procedure outlined by Chen et al. (2013) to present the first pharmaco-EEG ICA analysis of the resting-state EEG in healthy participants administered 0.45 mg/kg dexamphetamine. Twenty-eight healthy participants between 18 and 41 were recruited. Bayesian nested-domain models that explicitly account for spatial and functional relationships were used to contrast placebo and dexamphetamine on component spectral power and several connectivity metrics. Dexamphetamine led to reductions across delta, theta, and alpha spectral power bands that were predominantly localized to Frontal and Central regions. Beta 1 and beta 2 power were reduced by dexamphetamine at Frontal ICs, while beta 2 and gamma power was enhanced by dexamphetamine in posterior regions, including the parietal, occipital-temporal, and occipital regions. Power–power coupling under dexamphetamine was similar for both states, resembling the eyes open condition under placebo. However, orthogonalized measures of power coupling and phase coupling

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*Correspondence to: Matthew A. Albrecht; Maryland Psychiatric Research Center, Department of Psychiatry, School of Medicine, University of Maryland, Baltimore, 55 Wade Avenue, Catonsville,

MD 21228. E-mail: Matthew.Albrecht@curtin.edu.au, malbrecht@mprc.umaryland.edu

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did not show the same effect of dexamphetamine as power-power coupling. We discuss the alterations of low- and high-frequency EEG power in response to dexamphetamine within the context of disorders of dopamine regulation, in particular schizophrenia, as well as in the context of a recently hypothesized association between low-frequency power and aspects of anhedonia. *Hum Brain Mapp* 37:570–588, 2016. © 2015 Wiley Periodicals, Inc.

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INTRODUCTION

Resting-state networks are being increasingly studied in both healthy and psychiatric populations [Sporns, 2011]. Advances in EEG analysis, particularly blind source separation techniques [Delorme and Makeig, 2004] and measures of functional connectivity [Pascual-Marqui et al., 2011], have allowed a deeper investigation into these states. We here use a combination of advances in EEG analysis recently reported by Chen et al. [2013] to investigate a pharmacological manipulation of the resting-state network. Specifically, we evaluate the effect of the dopamine-, noradrenaline-, and (to a much lesser degree) serotonin-releasing agent, dexamphetamine, on the resting-state networks of the brain.

The dopamine-releasing property of dexamphetamine has made it a useful agent for investigating psychosis [Laruelle and Abi-Dargham, 1999; Abi-Dargham et al., 2009], and indeed, amphetamine-induced psychosis forms one of the major pillars of evidence for the dopamine model of schizophrenia [Howes and Kapur, 2009]. Dexamphetamine also possesses a range of desirable and performance enhancing effects. Dexamphetamine's ability to enhance motivation, attention, psychomotor activity, willingness to exert effort and to promote wakefulness [Martin-Iverson and Fawcett, 1996; Wyvell and Berridge, 2000, 2001; Wardle et al., 2011] has seen it used in a number of diverse situations ranging from flying air craft [Caldwell et al., 2003] to studying for exams [Hickman, 2010] and it is currently prescribed as a pharmacotherapy for attention-deficit hyperactivity disorder (ADHD). For these clinical and theoretical reasons, the effect of dexamphetamine on brain neurophysiology is of broad interest to practitioners and researchers.

Recently, Chen et al. [2013] applied a group ICA procedure to characterize the resting-state network of the EEG. The resultant temporally isolated EEG sources of the resting-state brain were grouped into five spatial clusters of EEG activity: Frontal, Central, parietal, occipito-temporal, and occipital. Using a simple alpha power-power coupling procedure, they demonstrated an increase in functional connectivity from the eyes closed to the eyes open state, particularly between posterior and anterior regions. In addition, they found that their alpha-band connectivity maps demonstrated some consistency with

resting-state networks derived from fMRI, such as the Default Mode Network (DMN) and the Dorsal Attention Network (DAN) [Fox et al., 2006]. For this study, we adopt a similar procedure to analyze the effects of dexamphetamine on the brain's resting-state networks.

There has been relatively little recent research evaluating resting-state networks of healthy populations acutely administered dopaminergic drugs. Generally, studies that administer amphetamines to humans [e.g., Fink et al., 1971; Hamilton et al., 1983] or other dopaminergic/psychostimulant agents to animals [Ferber et al., 1994; Timmerman and Abercrombie, 1996] show a reduction in low frequency cortical activity. However, there is little consistency within these studies on the effects of psychostimulants on higher frequencies and there has been little attempt to localize sources of resting-state EEG activity. The recent advances in EEG signal processing previously mentioned may be better able to identify the effects of dexamphetamine on cortical sources of human brain electrical activity, as well as to elucidate its effects on higher frequency activity. In addition, previous human studies have often used a very modest dose of amphetamine, where higher doses may give rise to more robust effects. For example, in a previous study [Albrecht et al., 2011a], we found substantial differences in the ERP profile within the same participants after given 0.45 mg/kg dexamphetamine relative to placebo, whereas previous studies using smaller doses [Halliday et al., 1994] have failed to find such effects.

The present study had two main aims. First, we attempted to replicate the resting-state group ICA, source localisation, and functional connectivity findings reported by Chen et al. [2013] using an expanded electrode array. Second, we characterized the effect of 0.45 mg/kg dexamphetamine administered to healthy participants on their resting-state EEG using the same group ICA and connectivity analyses. We hypothesized that the overall group ICA decomposition and source localization would approximate that found in Chen et al. [2013]. Furthermore, we anticipated that dexamphetamine would reduce slower oscillations consistent with previous studies that have administered psychostimulants (e.g., delta, theta, and alpha), while increasing higher frequency oscillations as in our previous studies on the effects of dexamphetamine on gamma ERPs (e.g., beta and gamma).

Figure 1.

Source localization and power spectra of each independent component derived from the group ICA procedure. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

METHODS

Participants

Twenty-eight healthy participants (14 female) between the ages of 20 and 48 were recruited ($M_{age} = 25$ years). Participants reported abstinence from alcohol for 24 h before testing and abstinence from other recreational drugs (other than nicotine) for 7 days. The mean participant weight was 71 kg and, with a dose of 0.45 mg/kg, yielded an average amount of dexamphetamine per person of 32 mg

dexamphetamine sulphate administered orally. Participants came to the center for two testing sessions, 1 week apart. The order that placebo and dexamphetamine were administered was counterbalanced: 14 participants received placebo on the first day and dexamphetamine on the second day, while 14 participants received dexamphetamine first and placebo second. The resting-state procedure testing began at 200 min post-dose, shortly after the reference peak dexamphetamine concentration for oral administration of 25 mg [Asghar et al., 2003]. This is also close to the peak time of the autonomic effects of

dexamphetamine [see, e.g., Figure 1 from Albrecht et al., 2011b]. Due to the complex relationships observed between heart rate and EEG [e.g., Lechinger et al., 2015; Dirlich et al., 1998], we report here the heart rate increase in response to amphetamine. Participants' heart rates were elevated by 7.6 bpm (95% HDI = 2.2, 13.4) during amphetamine administration (mean = 69.8 bpm, SD = 13.3) compared to placebo (mean = 62.2 bpm, SD = 10.2). Exclusionary criteria consisted of any psychiatric or neurological diagnosis, any cardiovascular disorder, epilepsy, a first-degree family member with schizophrenia, known hypersensitivity to amphetamines or hearing impairment. Reimbursement for participants was set at \$50 for completing each day of the study for a total of \$100 for the 2 days. Ethical approval was obtained from the University of Western Australia Ethics Committee and the North Metropolitan Area Mental Health Service Ethics Committee. The Australian and New Zealand Clinical Trials Registry number is ACTRN12608000610336. The cleaned EEG data presented in this paper, along with the Bayesian models described below, are available from the online data repository Zenodo (DOI: 10.5281/zenodo.33432).

Resting-State Procedure

Participants underwent two resting-state conditions: eyes open for 2 min followed by eyes closed for 4 min. Participants were instructed to relax as much as possible (to reduce muscle artefacts), limit eye movements, to keep their eyelids open or closed (depending on condition), and to fixate gently on a cross-hair displayed on computer monitor during the eyes-open condition.

EEG Recording and Preprocessing

The electroencephalograph (EEG) was recorded at 1,000 Hz with a Neuroscan 32-channel system according to the extended 10–20 system using an Ag/AgCl electrode cap that included vertical and horizontal electrooculograms. The online data were referenced to linked earlobes and the ground was positioned at electrode position AFz. Impedance for all channels was kept below 6 k Ω . The hardware bandpass filter was between 0.05 and 200 Hz. EEG data were imported into EEGLAB [Delorme and Makeig, 2004] for offline processing. Line (50 and 100 Hz) and computer monitor (75 Hz) electrical noise was reduced using the EEGLAB plugin “cleanline” [Mullen, 2012] and further bandpass filtered between 0.5 and 49 Hz. EEG recordings for each resting-state and drug administration condition were segmented into 2 s nonoverlapping epochs and baseline-corrected using the entire epoch. Epochs with large potential fluctuations were removed using EEGLAB's *pop_autorej* procedure (starting probability was set at 4 SD and the maximum % of epochs to reject per iteration was set at 6). The epochs were then downsampled to 500 Hz before the first independent components analysis (ICA)

decomposition using the infomax ICA algorithm [Bell and Sejnowski, 1995]. Horizontal and vertical eye artefact components were identified from the independent components (ICs) using the “corrmap” plugin [Viola, 2011], which computes the correlation between a reference scalp potential distribution and each of ICs in a dataset. The largest ICs representing one horizontal and one vertical eye movement artefact IC were removed from the EEG; the eye channels were then discarded. Further artefact rejection was carried out using the IC data, including (1) epochs with strong linear trends, (2) epochs with high joint probability of the component activity, (3) epochs with highly kurtotic activity (>5), (4) epochs with abnormal spectral power between 0–2 Hz and 20–40 Hz, and (5) epochs with voltages ± 100 μ V were also excluded.

The maximum number of epochs entered into the ICA was set at 60 epochs per person per condition to reduce the bias of oversampling epochs from the eyes closed condition. If a participant's data contained more than 60 usable epochs (which was likely for the eyes closed condition), 60 epochs were selected at random from all of the available nonrejected epochs. The average number of epochs used for the dexamphetamine and placebo conditions, respectively, were 57 (dexamphetamine) and 59 (placebo) epochs per person for the eyes closed condition and 49 and 45 epochs for the eyes open condition.

Group ICA

Following artefact rejection procedures on the individual EEG files, data were concatenated into one EEG dataset for a second group ICA decomposition. Group ICA on the concatenated files has been used previously by Chen et al. [2013] and Ponomarev et al. [2014], it is an extension of the ICA method used in fMRI research [Calhoun et al., 2001, 2009]. A total of 30 ICs were extracted (one per channel). Twelve ICs were deemed to be artefactual (unlikely to represent brain activity) on the basis of dipole location and power spectra, leaving 18 ICs for further analysis. There were five more components than that obtained by Chen et al. [2013], a result we attribute to the larger electrode array used in this study (30 vs 19 scalp electrodes). Average epoch-wise power of the back-reconstructed IC was calculated for each participant for each condition using Welch's modification to the Fast Fourier Transform (FFT) (1 s window size, no overlap).

Reliability of ICA decomposition

Several reliability coefficients of the group ICA decomposition were calculated including (1) split-half reliability within subjects—each participant's epochs were split into two halves and entered into the group ICA decomposition; (2) split-half reliability of all subjects and conditions, i.e., each condition (drug/placebo, eyes open/closed) for each participant was randomly assigned to two groups and each group entered independently into the group ICA

procedure; (3) split-half reliability by subjects—each subject was randomly assigned to one of two groups and data from all conditions was entered into gICA procedure. To calculate the reliability coefficients, the group ICA procedure was carried out for each subset of randomized data split according to the three methods outlined above. From the resultant ICA decomposition, the similarity between the mixing matrixes A^1 and A^2 can be calculated by

$$r_{ij}^{12} = \frac{|(A_i^1 A_j^2)|}{|(A_i^1)| |(A_j^2)|}$$

where i and j are the columns of matrices A^1 and A^2 , respectively. The maximal r_{ij}^{12} were arranged to fall on the diagonal of the matrix R . The similarity between A^1 and A^2 was calculated by

$$\hat{r} = \frac{\sum (r_{i=i})}{n}$$

the similarity index *rhat* equals 0.42 when A^1 and A^2 are random numbers sampled from a normal distribution and equal to 1 when A^1 and A^2 are equivalent. More details on these reliability analyses can be found in Ponomarev et al. [2014].

Source Localization (sLORETA)

Standardized Low-Resolution Electromagnetic Tomography (sLORETA) was used to localize each IC to an approximate cortical surface using the LORETA package [Fuchs et al., 2002; Pascual-Marqui, 2002]. sLORETA finds a 3D distribution of current source density given scalp recordings of brain electrical activity. IC scalp maps were exported from EEGLAB into LORETA. Channels were registered in LORETA using the inbuilt electrode localizations. The sLORETA inverse solution was calculated from the electrode registrations and applied to the IC scalp maps. The solutions were coregistered with the Talairach brain atlas [Talairach and Tournoux, 1988]. The brain image used for Figures 4–6 was derived from the Statistical Parametric Mapping MATLAB toolbox [Wellcome Trust Centre for Neuroimaging, 2009].

Spectral Analysis

We employed a novel statistical method that is able to model explicitly the relationships between components nested within regions. The method builds upon advances in hierarchical modelling in the Bayesian literature [Gelman and Hill, 2007; Gelman et al., 2012], culminating in the nested-domain model [Thurston et al., 2009]. The nested-domain model, as described by Thurston et al. [2009], was first applied within the neuropsychology literature to model effects of exposure and other biomarkers on cognitive performance. It was built on the principle that

individual measures within domains like episodic memory and executive functioning should be mutually informative both within and between domains to varying degrees. It is this property of hierarchical models that provides a solution to the multiple comparisons problem, leading to a reduction of Type M and Type S errors (rather than Type I and Type II errors). Type M errors are Magnitude errors that can be reduced through shrinkage inherent in hierarchical models and, to varying degrees, takes into account that subsequent effects reported in the literature are frequently smaller than the first reported effect. Type S errors are designated as Sign errors, which is finding evidence that indicates a positive effect when the true effect is negative and *vice versa*. This is in contrast to statistical methods that treat each measure within each domain as independent, e.g., Bonferroni corrections, which is unlikely to be the case with respect to the generation of brain oscillations.

One nested-domain model was constructed for the averaged power within each canonical frequency. Power bands were defined as delta (1–4 Hz), theta (4–8 Hz), alpha (8–12 Hz), beta 1 (12–20 Hz), beta 2 (20–30 Hz), and gamma (30–45 Hz). Dexamphetamine minus placebo difference scores, as the within-subjects contrasts of interest, were used as the dependent variable for the nested-domain model, i.e., power difference = (average power of Dexamphetamine for participant X, band Y, and resting-state condition Z) minus (average power of Placebo for participant X, band Y, and resting-state condition Z).

The domains within the nested domain model were organized spatially to approximately mirror the hierarchical structure presented in Chen et al. [2013]: ICs 1, 2, 3, and 4 were categorized as Frontal; ICs 5, 6, 7, 8, 9, and 10 were categorized as Central; ICs 11, 12, and 13 were categorized as Parietal; ICs 14 and 15 were categorized as Occipito-Temporal; and ICs 16, 17, and 18 were categorized as Occipital. The nested-domain model was structured as follows: (1) a whole brain effect for dexamphetamine for each resting-state condition (eyes open and eyes closed) was first estimated, (2) regional effects (i.e., Frontal, Central, Parietal, Occipito-Temporal, and Occipital) of dexamphetamine for each resting-state condition were then shrunk toward the whole brain estimate, and (3) individual IC effects (i.e., for ICs 1 through 18) of dexamphetamine for each resting-state condition were shrunk toward their regional contrast estimates. Note that while this method reduces differences between regions and components within regions, it is possible for an individual IC to retain its independence and deviate from the other ICs within that region if there is sufficient evidence.

The hierarchical structure of the Bayesian model described assumes the same nesting structure of electrical activity between placebo and dexamphetamine administration. We used this structure for several reasons: (1) it is optimal to base the nesting on an already established finding published in the literature; (2) the anatomical structure of the brain on amphetamine is the same as the brain on

placebo; and (3) there is consistency in the gICA decomposition across resting-state conditions between studies and across disorders; (4) there is good reliability between placebo and dexamphetamine for mixing matrices. However, it should be noted, the structure of the model allows the effect of dexamphetamine to differ in structure given sufficient evidence for a dissociation.

Model priors

More details on the model are provided in Supporting Information and the models are an extension of those used in previous publications [Chitty et al., 2014; Lam et al., 2013]. The prior for the overall effect of dexamphetamine was described by a normal distribution centered on 0 with a standard deviation equal to 1, i.e., it was anticipated that regardless of the direction of the effect of dexamphetamine, the effect size was most likely to be well within 1–2 standard deviations of the difference scores. Although this prior does not preclude larger effect sizes, larger effect sizes require more evidence and would be shrunk towards 0. The regional deviation priors were described by a normal distribution centered on the overall effect and with a standard deviation (SD) estimated from a half-Cauchy prior centered on zero and scale equal to 1 (this controls the amount of shrinkage, with a large SD leading to less shrinkage compared with a smaller SD). The prior for the individual IC deviations from the regional effect was described by a normal distribution centered on the regional effect and with an SD estimated from a half-Cauchy prior centered on zero and scale equal to 1. The residuals were modeled by a *t*-distribution with the degrees of freedom parameter set at 4 to render the analysis more “robust” [Lange et al., 1989; Kruschke, 2013]. *t*-distributions are fatter tailed versions of the normal distribution where the degrees of freedom parameter (df) controls the “fatness” of the tails. An infinitely large df parameter renders the distribution equivalent to a normal distribution, while a df of 4 renders the distribution fatter-tailed thereby down-weighting distant values in the tails. Setting the df rather than estimating the df from the data is a compromise between statistical and computational efficiency. The prior for the SD of the residuals/likelihood for each component within the model was described by a uniform distribution bounded by 0 and 5.

Connectivity Analysis

Epoch-wise power across all frequency bands analyzed was correlated across the 18 ICs per drug and resting-state condition by participant, to yield a power-power coupling connectivity matrix to match the functional connectivity analysis used in Chen et al. [2013]. Connectivity matrices underwent Fisher’s *r* to *z* transformation (i.e., $z = \text{arctanh}[r]$) before being averaged across drug and resting-state conditions. Lines indicating connectivity on the figures were first filtered by excluding connectivity where

the credible interval included 0 (see below for model) and were then weighted by the size of the connectivity between the two ICs.

A hierarchical model similar to that used for the frequency power contrasts was used to contrast the drug effect on connectivity between components. The model was structured such that dexamphetamine—placebo correlation contrasts took advantage of the domains outlined above. For example, correlation contrasts for the Frontal ICs were coded as “1–1,” and correlation contrasts between Frontal ICs and Central ICs were coded as “1–2” and so on for all other combinations. This gave a total of 15 domains, i.e., 5 domains for the connectivity contrasts within a region (Frontal–Frontal) and 10 domains for the connectivity contrasts between regions (Frontal–Central). The top 5% by effect size of the contrasts are shown. The analysis code is provided in Supporting Information.

Orthogonalized Measures of Connectivity

Despite the gICA procedure significantly reducing the mutual statistical dependency between signals compared to channel data [Ponomarev et al., 2014], we implemented two measures of connectivity that are resistant to the effects of volume conduction: (1) the debiased weighted phase lag index (DWPLI) described in Vinck et al. [2011] and (2) the orthogonalized power envelope correlation described in Hipp et al. [2012].

Orthogonalized power envelope correlation

Orthogonalized measures that utilize the imaginary part of coherency and hence remove synchronization with zero phase lag represented by the real part of coherency were proposed to minimize the effects of volume conduction and the use of a common reference on connectivity measures [Nolte et al., 2004]. We applied the orthogonalized power envelope correlation method [Hipp et al., 2012] to the Hilbert transformed gICA activations for each participant, drug condition, and resting-state condition. gICA activations were bandpass filtered (linear phase shift, 5 dB reduction over 0.5 Hz) for each frequency band according to the spectral widths defined above. The resulting filtered activations were Hilbert transformed, yielding a time–frequency estimation, $X(t,f)$, for each time point and frequency band across epochs. Orthogonalization for each pair of signals, $X(t,f)$ and $Y(t,f)$, was carried out at each time point by first removing the signal from $Y(t,f)$ that possesses zero phase lag with signal $X(t,f)$ (as signals with zero phase lag are most likely due to volume conduction) using the following formula [from Hipp et al., 2012]:

$$Y_{\perp X}(t,f) = \Im \left(Y(t,f) \frac{X(t,f)^*}{|X(t,f)|} \right)$$

The orthogonalized signal $Y_{\perp X}(t,f)$ and its pair $X(t,f)$ were squared and $\log_{10}$ transformed before estimating the

Figure 2.

Standardized component power contrasts. Dexamphetamine minus placebo power contrasts (+95% HDIs) obtained from the hierarchical nested domain model for each independent component. Credible effects are denoted by the 95% HDI excluding 0 ($N = 28$). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

correlation coefficient (Pearson's r) between the two signals within each epoch and finally averaged within each person by drug administration state and resting-state condition. Note the Orthogonalization of power signals goes both ways, i.e., from $Y(t,f)$ to $X(t,f)$ and from $X(t,f)$ to $Y(t,f)$. Both directions were averaged to obtain a single power-coupling metric.

Debiased weighted phase lag index (DWPLI) square estimator

The DWPLI is an extension of phase synchronization methods described by Nolte et al. [2004] and Stam et al. [2007]. Stam et al. [2007] improved on this measure of synchronization by introducing the phase lag index (PLI).

The PLI takes the expectancy of the sign of the imaginary part of coherency, thereby reducing the dependence of the synchronization metric on the phase of the two signals. The DWPLI improves on the PLI by weighting the PLI by the magnitude of the imaginary part of coherency. DWPLI - $\hat{\Omega}^w$ - is defined as follows [equation 31 from Vinck et al., 2011]:

$$\hat{\Omega}^w \equiv \frac{\sum_{j=1}^N \sum_{k \neq j} \Im(X_j) \Im(X_k)}{\sum_{j=1}^N \sum_{k \neq j} |\Im(X_j) \Im(X_k)|}$$

where X_j and X_k are the complex valued cross-spectra of trials j and k , respectively. The Field Trip toolbox [Oostenveld et al., 2011] was used to calculate the DWPLI. DWPLI

Figure 3.

Standardized channel power contrasts. Dexamphetamine minus placebo power contrasts (+95% HDIs) obtained from the hierarchical nested domain model for the channel data. Credible effects are denoted by the 95% HDI excluding 0 ($N = 28$). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

values were averaged over each frequency band across participant and drug administration state, and then entered into the Bayesian hierarchical model already described for the connectivity analysis.

Frequentist Type I Error Properties of the Analytic Method

While the Type I error rate is more of a concern within the context of Frequentist analyses, we describe here a simulation to characterize the Type I error properties of the hierarchical Bayesian method as used in the present circumstances. A permutation style approach was applied using data from each of the different frequencies and anal-

yses (power contrast, amplitude power coupling, DWPLI, orthogonalized power envelope correlation, and graph theoretic analyses) by randomizing the sign of the respective metric, i.e., the Dexamphetamine-Placebo contrast value was randomly multiplied by either +1 or -1. This was repeated 1,000 times for the power contrast model, 100 times for the connectivity models, and 1000 times for each the graph theoretic analyses on the different connectivity metrics. This gave a total of 36,000 comparisons for the component power model, 30,600 comparisons for each of the power-coupling, orthogonalized power coupling, and DWPLI models, and 144,000 comparisons for the graph theoretic analyses. The nominal Type I error rates were very low. For each simulation, there were only 36/36,000

Figure 4.

Power-power coupling. Left: power-power connectivity matrices for the eyes closed (above the diagonal red line) and eyes open (below the diagonal red line) resting-state conditions for placebo and dexamphetamine. Presented are the raw correlations or connectivity metrics averaged over each condition. Right: connectivity maps for the eyes closed and eyes open resting-state conditions for placebo and dexamphetamine. For

the noncontrast maps, the lines are filtered at $p < 0.0001$. For the contrast maps, the lines are filtered based on the 95% HDI from the hierarchical Bayesian model excluding 0. See methods for Type I error properties of this method ($N = 28$). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

(power component contrast), 2/30,600 (component power coupling), 0/30,600 (component orthogonal power coupling), and 0/30,600 (DWPLI component connectivity) comparisons where the 95% CI excluded 0.

For the power-contrast analyses presented in Figures 2 and 3 and for the connectivity analyses presented in Figures 4–6, there was one model estimated per frequency and analysis type ([component and channel] or [power-power coupling, orthogonalized power coupling and DWPLI]), with each model including all spatial locations and resting-state conditions in the correction. This was also true for the corresponding Type I error approximation. The Type I analysis above corresponds to a nominal type I error rate of approximately 0.001 for each power analysis set (Figs. 2 and 3), while the nominal rate for the connectivity analysis was approximately less than 0.00006 per set (Figs. 4–6). Last, in the analyses in Figure 7, there were 12 contrasts per set, where a set included one connectivity metric, one graph metric, all frequencies, and both resting-state conditions. A similar permutation analysis indicated an average Type I error rate of 0.0038.

Graph-Theoretic Network Metrics

We supplemented the connectivity results above with several measures derived from Graph-Theory: (1) clustering coefficient, (2) modularity, (3) characteristic path length, and (4) global efficiency. Clustering coefficient and modularity are thought to reflect the functional segregation properties of a complex network, while characteristic path length and global efficiency are thought to reflect functional integration of a complex network [Sporns, 2011]. The measures were calculated on the weighted connectivity matrices (thresholded from 10% to 50% of the connections in steps of 2.5%) using the Brain Connectivity Toolbox [Rubinov and Sporns, 2010] in MATLAB. Again, measures were obtained for each participant for all drug and resting-state conditions and for all frequencies and connectivity metrics. Dexamphetamine-Placebo contrast values were entered into Bayesian hierarchical models, with one hierarchical model per graph theoretic metric and connectivity measure, i.e., the analysis for the DWPLI clustering coefficient included the Dexamphetamine-

Figure 5.

Orthogonalized power–power coupling. Left: orthogonalized power–power connectivity matrices for the eyes closed (above the diagonal red line) and eyes open (below the diagonal red line) resting-state conditions for placebo and dexamphetamine. Presented are the raw correlations or connectivity metrics averaged over each condition. Right: connectivity maps for the eyes

closed and eyes open resting-state conditions for placebo and dexamphetamine. For the noncontrast maps, the lines are filtered at $p < 0.0001$. For the contrast maps, the lines are filtered based on the 95% HDI from the hierarchical Bayesian model excluding 0 ($N = 28$). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Placebo contrast for all frequencies and both resting-state conditions. We should note that the optimal way to convert imaging data to matrices for graph analysis is uncertain [Stam and Reijneveld, 2007]. One potential issue arising from orthogonalized connectivity corrections for graph theoretic analyses is that the correction produces multiple unique signals at each vertex due to removal of the shared activity being unique for each edge. However, measures that do not account for volume conduction and common reference effects lead to the overestimation of local connections [Christodoulakis et al., 2015]. We have calculated the graph theoretic metrics for all three of the connectivity methods to allow comparison.

Statistical Software

All statistical analysis was conducted in R version 3.1.2 [R Development Core Team, 2013], using the “rstan” package [Stan Development Team, 2013] for Hamiltonian Monte Carlo sampling, a form of Markov chain Monte Carlo sampling. All models were run using 4 chains of 5,000 samples each. The first 2,500 samples of each chain were discarded

as burn-in and adaptation. Convergence was monitored using the Gelman–Rubin statistic [Gelman and Rubin, 1992] and the total number of effective samples per parameter of interest was $>2,000$. Highest density intervals (HDI) of 95% were used for inference and figure presentation [Kruschke, 2011]. Similar to Frequentist confidence intervals, credible intervals that exclude 0 are taken to be “credibly different to 0.”

RESULTS

ICA Decomposition

A total of 18 components were extracted from the group ICA procedure. Figure 1 illustrates the sLORETA source estimations and spectral power of the selected components. Table I provides the Talairach coordinates obtained from the dipole fitting procedure. A number of current source densities obtained by sLORETA are consistent with the Brodmann areas of the fitted dipoles obtained by Chen et al. [2013]. The reliability coefficients for the group ICA decomposition were high: split-half reliability within

Figure 6.

Debiased weighted phase lag index (DWPLI). Left: DWPLI connectivity matrices for the eyes closed (above the diagonal red line) and eyes open (below the diagonal red line) resting-state conditions for placebo and dexamphetamine. Presented are the raw correlations or connectivity metrics averaged over each condition. Right: connectivity maps for the eyes closed and eyes

participants (50% epochs for each person entered into separate group ICA) was 0.997 (SD = 0.001); split-half reliability for all participants and conditions was 0.93 (SD = 0.02); split-half reliability by participant was 0.89 (SD = 0.02).

Spectral Differences between Dexamphetamine and Placebo

Figure 2 presents the standardized dexamphetamine–placebo contrasts from the Bayesian nested domain model for each frequency across resting-state conditions and ICs (Supporting Information, Fig. 1 presents the same model contrasts but reverted back to the original scale of the data). Most notable is a broadband reduction of slower frequencies in Frontal and Central ICs, including reductions in delta, theta, and alpha frequencies for both resting-state conditions. Delta and theta frequencies were reduced to a lesser extent at Parietal, Occipito-Temporal and Occipital regions.

For the higher frequency parts of the spectra, both beta frequencies (beta 1 and beta 2) showed reductions in power after dexamphetamine in Frontal regions. By contrast, beta 2 and gamma frequencies were increased in Parietal, Occipital-Temporal and Occipital regions in response to

open resting-state conditions for placebo and dexamphetamine. For the noncontrast maps, the lines are filtered at $p < 0.0001$. For the contrast maps, the lines are filtered based on the 95% HDI from the hierarchical Bayesian model excluding 0 ($N = 28$). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

dexamphetamine. This was most notable during the eyes open condition although the interaction contrasts did not indicate strong differences between eye conditions.

Figure 3 presents the power differences between dexamphetamine and placebo for the channel data (Supporting Information, Fig. 2 presents the same model contrasts but reverted back to the original scale of the data). Spectral differences between dexamphetamine and placebo in the channel data were comparable to the differences in the IC decomposed data. For example, the channel data showed reductions in delta and theta frequencies, as well as increases in beta and gamma frequencies. However, the effects of dexamphetamine in these frequencies did not match the regional differences from the ICA decomposition. This is to be expected as the IC decomposed data possesses better regional localization compared with the raw channel data. Moreover, the strength of artefactual activity is likely to be stronger in the channel data compared to the brain restricted IC data.

Resting-State Connectivity

The left side of Figures 4–6 presents the raw connectivity matrices for each of the connectivity methods used.

Figure 7.

Graph theoretic metrics. Dexamphetamine-placebo contrast estimates for each graph theoretic metric. Presented are the means and 95% HDI obtained from the hierarchical Bayesian model. Credible effects are denoted by the 95% HDI excluding 0 ($N = 28$). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

The right side of Figures 4–6 presents the connectivity maps with significant connections between ICs for each of the conditions (filtered by $p < 0.0001$) along with the dexamphetamine-placebo contrast results from the Bayesian Hierarchical model (filtered based on the 95% credible interval excluding 0).

Power–power coupling

As can be seen in Figure 4, the largest connectivity was seen in the theta, alpha, and beta1 bands within the eyes closed condition. Dexamphetamine reduced power–power coupling within each of these three band and was most notable in the alpha band for ICs sourced in the parietal cortex. The effect of dexamphetamine on power–power coupling was reduced in the eyes-open resting-state condition. Interestingly, there was also an increase in gamma

power connectivity, most notable in the eyes-closed condition.

Orthogonalized power coupling

Figure 5 presents the orthogonalized power–power coupling between ICs. Compared to the nonorthogonalized power coupling connectivity, there was no discernible influence of dexamphetamine on brain connectivity using this metric. A similar pattern of connectivity differences between resting-state conditions was observed using the orthogonalized measure of connectivity compared to the nonorthogonalized measure, e.g., there was more connectivity during the eyes-closed condition compared to the eyes-open condition. Both gamma and delta connectivity were attenuated in comparison to the nonorthogonalized power-coupling measure.

TABLE I. Talairach coordinates obtained from the dipole fitting procedure

Component	<i>x</i>	<i>y</i>	<i>z</i>	BA	Region	Cluster
1	5	40	16	BA32	Anterior cingulate	Frontal
2	−5	32	54	BA6	Superior Frontal gyrus	Frontal
3	−50	16	27	BA9	Middle Frontal gyrus	Frontal
4	50	16	27	BA9	Middle Frontal gyrus	Frontal
5	−5	−7	56	BA6	Medial Frontal gyrus	Central
6	−59	−3	37	BA6	Precentral gyrus	Central
7	59	−3	32	BA6	Precentral gyrus	Central
8	5	−40	67	BA5	Postcentral gyrus	Central
9	−35	−36	57	BA5	Postcentral gyrus	Central
10	40	−41	62	BA5	Postcentral gyrus	Central
11	5	−66	49	BA7	Precuneus Parietal	Parietal
12	−35	−56	44	BA40	Inferior parietal lobule	Parietal
13	50	−57	30	BA39	Superior temporal gyrus	Parietal
14	−59	−48	12	BA22	Superior temporal gyrus	Occipito-Temporal
15	59	−53	12	BA22	Superior temporal gyrus	Occipito-Temporal
16	5	−97	9	BA18	Cuneus	Occipital
17	−35	−83	−8	BA18	Middle occipital gyrus	Occipital
18	30	−92	5	BA18	Middle occipital gyrus	Occipital

Debiased weighted phase lag index (DWPLI) square estimator

Figure 6 presents the orthogonalized phase–phase coupling metric: DWPLI. In contrast to the power-coupling measures above, DWPLI was increased after dexamphetamine administration. This effect was largest in the alpha and theta frequency bands. In addition, DWPLI connectivity was reduced during the eyes-open condition compared to the eyes-closed condition—a result that was also present for the previous power coupling analysis.

Graph theoretic measures

Figure 7 presents the scaled contrast estimates (dexamphetamine–placebo) obtained from the hierarchical Bayesian models for each connectivity measure and graph theoretic metric: clustering coefficient, modularity, characteristic path length, and network efficiency. Dexamphetamine led to a reduction in the theta power-coupling clustering coefficient during the eyes-closed condition, which was attenuated when the orthogonalization metric was applied. Interestingly, the clustering coefficient was enhanced at alpha and beta1 for DWPLI. Similarly, power–power coupling characteristic path length was increased by dexamphetamine during eyes-closed, but again this was attenuated when orthogonalized and credibly enhanced for the DWPLI. These results suggest that dexamphetamine modifies selective elements of complex resting-state network organization.

DISCUSSION

To our knowledge, this is the first report of a group ICA decomposition and localization of resting-state EEG com-

ponents that has been applied in a psychopharmacological context using the method recently outlined in Chen et al. [2013]. Dexamphetamine actively promotes the release of catecholamines within the major dopaminergic and noradrenergic bundles in the brain. These catecholaminergic systems are critically involved in a range of experiences, behaviors, and psychiatric disorders.

Dexamphetamine and Oscillatory Activity

Administration of 0.45 mg/kg dexamphetamine to healthy volunteers led to reductions in power across delta, theta and alpha frequency bands that were predominantly localized to Frontal and Central Regions. In addition, power also modestly reduced for delta and theta frequencies at posterior ICs. The reduction of slower frequencies was not specific for a particular resting-state condition. The effects of dexamphetamine on the higher frequencies were more complex. Power was reduced within both the beta 1 and beta 2 bands by dexamphetamine at Frontal ICs, while beta 2 and gamma power was enhanced by dexamphetamine in posterior regions, including the Parietal, Occipital-Temporal, and Occipital regions. Again, there was not strong evidence for a substantial difference between resting-state conditions.

Relatively few studies of the acute effects of catecholaminergic agents on the healthy human EEG have been reported. Early work by Fink et al. [1971] showed reductions in delta power after 10 mg of dexamphetamine. However, there was no localization of affected sources in their study. In contrast, Hamilton et al. [1983] demonstrated increases in the alpha and beta frequency ranges after 10 mg of dexamphetamine and no effects were noted for other frequency bands. However, Hamilton et al. [1983] only recorded from two electrode positions (Fz and

Pz). The preclinical animal work on catecholaminergic effects on the EEG is consistent with the results in the current article, particularly with studies administering amphetamine [Ferber et al., 1994; Stahl et al., 1997] and other psychostimulants [Ferber et al., 1994]. In particular, Frei et al. [2001] administered 3,4-methylenedioxy-N-methylamphetamine (MDMA), an amphetamine with more potent serotonin releasing properties compared with dexamphetamine, to healthy human volunteers and found a reduction in Frontal delta and a widespread reduction theta power, similar to the effects seen in the present study. In contrast, the effect of MDMA on beta power was an increase in Frontal regions and a reduction in posterior regions, opposite to that seen in this study. Similarly, the effect of MDMA on alpha was a reduction in power localized to posterior regions while dexamphetamine reduced alpha power in more Frontally located components. The contrast of these two studies potentially highlights the differences in the EEG power spectra profile that results from the removal (or addition) of the serotonergic component of amphetamine type stimulants.

The preclinical work offers some potential targets for the role of enhanced catecholaminergic transmission on the EEG. Direct electrical stimulation of the ventral tegmental area (a region with a high concentration of dopamine neurons) resulted in a reduction of delta oscillations in the nucleus accumbens [Leung and Yim, 1993]. Several rat studies have shown that the dopamine D₁ receptor may be especially involved in reducing the power of low frequency EEG components. These studies have used the dopamine D₁ receptor agonist SKF38393, systemic administration of amphetamine (0.4 mg/kg) and injection of amphetamine directly into the substantia nigra to show consistent reductions of low-frequency EEG power spectra [Kropf and Kuschinsky, 1993; Ferger et al., 1994; Timmerman and Abercrombie, 1996]. All three studies used the dopamine D₁ receptor antagonist SCH23390 to block the effects of SKF38393 and amphetamine on the EEG [Kropf and Kuschinsky, 1993; Ferger et al., 1994; Timmerman and Abercrombie, 1996]. Furthermore, haloperidol, a dopamine D₂ receptor antagonist, failed to block the effect of amphetamine on the EEG [Ferber et al., 1994]. Larger doses of dexamphetamine (4 mg/kg) resulted in increased alpha power, which the authors suggested was due to D₂ activation [Ferber et al., 1994] because of their earlier work using the dopamine D₁ and D₂ receptor agonist apomorphine [Kropf and Kuschinsky, 1993]. Interestingly, a sensitization regime that repeatedly administered a lower dose of dexamphetamine caused an increase in power in the alpha1 band, suggesting that D₂ receptors are involved in sensitization effects seen in rat EEG [Stahl et al., 1997]. With respect to the results in this study, reductions of delta and theta frequencies are likely related to enhanced activation of dopamine D₁ receptors, if the rodent data can be extrapolated to the human case.

Dexamphetamine influences noradrenergic transmission to an equal, or even greater, degree than dopaminergic

transmission. Locus coeruleus (the major noradrenergic bundle) activation in rats results in a shift from low-frequency high-amplitude oscillations to high-frequency low-amplitude oscillations in Frontal areas [Berridge and Foote, 1991]. Similarly, combined administration of alpha1 and beta noradrenergic receptor antagonists in rats results in an increase in power of low-frequency oscillations [Berridge and España, 2000]. Therefore, we cannot definitively determine whether noradrenergic transmission or dopaminergic transmission is the cause of the spectral power profile induced by dexamphetamine. However, dopamine D₁ receptor activation, rather than D₂ activation, and LC stimulation are both consistent with the EEG profile of dexamphetamine.

Comparison to Previous Research

Given the novelty of the analysis techniques used, it is informative to compare our findings with those of Chen et al. [2013]. Our findings demonstrated general consistency with Chen et al. [2013], with several overlapping ICs localized to similar regions by sLORETA. This is despite having relatively few electrodes for source localization in both the present study and in Chen et al. [2013]. We believe that this shows the strength of the method by Chen et al. [2013] and the group ICA procedure and offers a viable alternative to clustering algorithms that have been used to cluster separate ICs from different individuals [Delorme and Makeig, 2004]. We only noted subtle differences between scalp topographies and eventual source localizations, and most of the differences appear to be the result of having more electrodes in this study. For example, IC9 and IC10 (localized approximately to BA5) in this study were not present in Chen et al. [2013] and this resulted in some slight shifts in the localization and frequency profile as the electrical activity became better separated and localized.

One notable difference between Chen et al. [2013] and this study is seen in the functional connectivity analysis. Chen et al. [2013] found strong enhancements in functional connectivity during the eyes open state compared to the eyes closed condition. By contrast, in the placebo condition, which would be most comparable with Chen et al. [2013], we found strong enhancements in alpha functional connectivity in the eyes closed condition compared to the eyes open condition. One possibility for this conflicting result is the ordering of the resting-state conditions: in both studies, the resting-state condition that was experienced second (eyes open in Chen, eyes closed in this study) was the condition with the most alpha functional connectivity. In both studies, eye condition was confounded by order. Future studies should counterbalance the eyes open/closed conditions.

EEG Power and Dopaminergic Disorders

The findings presented here can be contrasted with those seen in disorders that have been hypothesized to

relate to dopamine regulation or disorders that are currently treated with dopaminergic agents (e.g., schizophrenia, ADHD, Parkinson's, methamphetamine withdrawal, and aspects of anhedonia that relate to reward/motivation). Each of these disorders has been identified as having an elevated power profile of low frequency activity, namely increases in resting-state delta and theta [Barry et al., 2003; Newton et al., 2003; Hermens et al., 2005; Bresnahan et al., 2006; Stoffers et al., 2007; Moazami-Goudarzi et al., 2008; Wacker et al., 2009; Woltering et al., 2012] and at the same time, a reduction in event-related delta and theta power [e.g., for schizophrenia, see Ford et al., 2008; Donkers et al., 2013]. Furthermore, studies in patients with Parkinson's and ADHD who are administered dopaminergic agents (e.g., L-DOPA, methylphenidate and amphetamine) have found a relative normalization of delta and theta frequencies [Hermens et al., 2005; Bresnahan et al., 2006; Stoffers et al., 2007; Woltering et al., 2012]. Interestingly, schizophrenia is the only disorder mentioned that has a well-characterized enhancement of dopamine activity (rather than a putative reduction in dopamine activity) and is treated with dopamine antagonists as opposed to dopamine-enhancing agents. Importantly, the review and meta-analysis by Boutros et al. [2008] found enhancements in delta and theta frequencies in a subset of unmedicated patients with schizophrenia [Boutros et al., 2008].

In contrast to the low-frequency profiles of these disorders, the higher frequency resting-state profiles have been far less well characterized. In patients with schizophrenia, increases in beta and gamma frequencies have been found during resting-state [Morstyn et al., 1983] or prestimulus periods [Spencer, 2011], which appear to be similar in some respects to the high-frequency effects of dexamphetamine found in this study (i.e., increases of beta and gamma at posterior and occipital-temporal sites). Lee et al. [2006] recorded resting EEG in patients with persisting auditory hallucinations compared EEG power with patients who had not experienced auditory hallucinations for at least 2 years and found significant increases in high frequency activity in parietal and medial Frontal gyrus regions in the auditory hallucinating group. A similar finding of increased high-frequency MEG activity in the auditory cortex was reported in an individual who was currently experiencing auditory hallucinations [Ropohl et al., 2004]. We found dexamphetamine-induced enhancements at gamma frequencies both to phasic gamma activity during auditory steady-state responses [Albrecht et al., 2013] and to gamma activity that occurs around the peak of the P300 ERP [Albrecht et al., 2012]. We have previously hypothesized a number of links between elevated synaptic levels of dopamine, increased gamma and positive psychotic symptoms [Albrecht et al., 2012, 2013] that builds upon several findings in the literature from patients with psychosis and the relevant discussions from the respective authors [Gordon et al., 2001; Lee et al., 2003; Spencer et al., 2008, 2009]. These findings may be useful in understand-

ing what role endogenous dopamine and/or noradrenergic hyperactivity has on the electrophysiological signs of schizophrenia, and what signs may perhaps be better explained by alterations in different transmitters systems, alterations in neurological architectures, or which signs might be a consequence of the chronic administration of antipsychotic medications. However, it should be noted that the increased gamma power may be due to residual motor artefact not adequately removed from the group ICA procedure.

With respect to the motivational aspects of low-frequency activity and dopamine, Knyazev [2012] hypothesized that low-frequency oscillations, particularly delta oscillations, are related to the brain reward system, attention, and salience detection. Knyazev [2012] reviews a number of lines evidence indicating that delta oscillations depend upon core reward-related circuitry including the VTA, the nucleus accumbens, the medial prefrontal cortex, and the nucleus reticularis thalami. Furthermore, he cites evidence from drug dependence, obesity, anhedonia, and the preclinical motivational literature suggesting that the "...it appears that need for reinforcement increases delta oscillations, whereas actual reinforcement causes their decrease." [Knyazev, 2012, p.688]. From this perspective, the reduction in low-frequency activity by dexamphetamine may indicate a state of satiated reinforcement. This is consistent with findings indicating that one of the major sources of resting-state delta oscillations, the rostral anterior cingulate cortex (MNI co-ords: $x = 4, y = 38, z = 1$), together with nucleus accumbens reward responsivity have been associated with anhedonia in humans [Wacker et al., 2009]. These MNI coordinates overlap substantially with IC1 in this study localized to BA32 (MNI: $x = 5, y = 40, z = 16$), and the Frontal components show the most reduction by dexamphetamine in the lower frequencies.

Connectivity Effects of Dexamphetamine

In contrast to the frequency power profile of dexamphetamine, there was a modest reduction in theta, alpha, beta1, and beta2 power-coupling after the administration of dexamphetamine that was restricted predominantly to the eyes-closed (second) condition. Indeed, the functional connectivity maps representing the eyes-closed and eyes-open conditions appear very similar between conditions after dexamphetamine. By contrast, the connectivity maps for the placebo condition indicated elevated connectivity in the theta, alpha, and beta1 bands during the eyes-closed (second) condition compared with the eyes-open (first) condition. Chen et al. [2013] suggest that the connectivity patterns are consistent with the resting-state networks found in fMRI studies; specifically, the DMN and DAN [Fox et al., 2006]. Consequently, it appears as though dexamphetamine maintains a resting-state network throughout the experiment that resembles a more alert state.

Compared to the straight power–power coupling measure, the orthogonalized version attenuated connectivity and reduced the differences between dexamphetamine and placebo. As the orthogonalized metric reduces spurious connectivity by eliminating the shared signal due to volume conduction and the use of common reference, the differences between placebo and dexamphetamine may be due to overall power differences and not necessarily due to differences in connectivity. Indeed, even after applying spatial filtering to EEG data it is still advised to use a connectivity measure that is resistant to volume conduction [Cohen 2015]. However, this may not be able to account for all connectivity differences because there is not a consistent increase in alpha activity over all components. Some of the strongest power-coupling connectivity differences are seen in the alpha band in the parietal regions, which do not appear to be strongly influenced by dexamphetamine (see Fig. 2). Other methods of orthogonalizing power connectivity metrics have recently been proposed that improve the identifiability of power coupling networks. For example, Colclough et al. [2015] outline a strongly performing symmetric orthogonalized power coupling metric that resolves the potential confounding issue of asymmetrical connectivity. Their symmetric method further attenuates spurious connectivity compared to nonsymmetric approaches similar to that used in this article (although the nonsymmetric method still performed relatively well), and would likely also show a reduction in power-coupling compared to the nonorthogonalized version used here.

In contrast to power coupling, orthogonalized phase connectivity (DWPLI) was increased after dexamphetamine administration, particularly in the theta and alpha frequency bands. Increases in phase connectivity in the alpha band is associated with multisensory integration [van Driel et al., 2014], separates minimally conscious patients from vegetative state patients [Lehembre et al., 2012], and is reduced in Alzheimer’s disease [Stam et al., 2009] suggesting an enhancement of function on resting-state networks by dexamphetamine. Similarly, increases in alpha band DWPLI clustering coefficient [Stam et al., 2009; Chennu et al., 2014] and reductions in alpha band characteristic path length [Chennu et al., 2014] have been associated with improved mental state. Moreover, recent studies suggest that theta phase-coupling between fronto-parietal cortex may be a Central mechanism of executive function and general cognitive performance [Mizuhara and Yamaguchi, 2007; Kawasaki et al., 2010; Polanía et al., 2012]. Consequently, these increases in theta and alpha phase-coupling may explain the improvements in cognitive performance observed after administration of dopaminergic psychostimulants [Spencer et al., 2015].

Statistical Methods

We present a novel method of statistical analysis that we believe more appropriately represents the relationship

between separate brain components of the EEG. Although hierarchical models are not restricted to the Bayesian paradigm, the nested-domain hierarchical model used here was developed within the context of the Bayesian paradigm [Thurston et al., 2009] and presents a powerful and flexible method of accounting for dependencies in the data. Alternative methods of correcting for multiple comparisons such as Bonferroni or False Discovery Rate FDR [Benjamini and Hochberg, 1995] are often used in order to reduce the Type I error rate of multiple tests. However, alpha levels for significance can quickly escalate (note especially the number of corrections that could be suggested to correct for the functional connectivity analysis) and this approach fails to take into account the spatial and functional relationships that are likely to exist between different ICs. Furthermore, an assumption of the Bonferroni is that the tests should be considered as being independent of each other. However, this assumption is unlikely given the small world architecture of the cortex [Sporns, 2011]. It is also pleasing to note that the hierarchical Bayesian method performs well in reducing Type I error, as shown by the permutation-style analysis.

The hierarchical structure used in this analysis reflects the assumption that power within a frequency BAnd from one IC will be influenced to a similar degree by dexamphetamine as other ICs in that same anatomical region (regional shrinkage). Similarly, a weaker assumption (reflected in the model) is that regions may be affected to a similar extent as an effect of dexamphetamine on the whole brain (global shrinkage). This does not mean that the hierarchy completely constrains the differences that can be identified. Rather the model requires stronger evidence to dissociate a single component within a region and weaker evidence to dissociate a region from the overall effect within the whole brain. Indeed, the analysis presented here shows that there do appear to be differential regional effects of dexamphetamine.

Conclusions

Catecholamine systems play an integral role in behavior and dysfunction of these systems can result in disabling psychiatric disorders. We present the first report of this method applied in a psychopharmacological context using the recently published group ICA decomposition outlined by Chen et al. [2013]. Dexamphetamine led to reductions across delta, theta, and alpha spectral power bands that was predominantly localized to Frontal and Central Regions that were not specific for a particular eyes open or eyes closed resting state. By contrast, beta 1 and beta 2 power was reduced by dexamphetamine at Frontal ICs, while beta 2 and gamma power was enhanced by dexamphetamine in posterior regions, including the Parietal, Occipital-Temporal, and Occipital regions. Connectivity analyses revealed decreased power–power coupling across the cortex under dexamphetamine, but increased phase–

phase coupling. This dissociation of connectivity metrics may reflect differential effects on the ability of dexamphetamine to influence neural timing across the cortex. These findings have significant implications for interpreting resting-state functionality in disorders and dopamine dysfunction and disorders that are treated with dopaminergic agents.

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