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Evaluating the Resource Allocation Index as a Potential fMRI-based Biomarker for Substance Use Disorder

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Abstract

Background—There is a lack of neuroscience-based biomarkers for the diagnosis, treatment and monitoring of individuals with substance use disorders (SUD). The resource allocation index (RAI), a measure of the interrelationship between salience, executive control and default-mode brain networks (SN, ECN, and DMN), has been proposed as one such biomarker. However, the RAI has yet to be extensively tested in SUD samples.

Methods—The present analysis compared RAI scores between individuals with stimulant and/or opioid use disorders (SUD; $n = 139$, abstinent 4–365 days) and healthy controls (HC; $n = 56$) who had completed resting-state functional magnetic resonance imaging (fMRI) scans within the context of the Tulsa 1000 cohort. First, we used independent component analysis (ICA) to identify the SN, ECN, and DMN and extract their time series data. Second, we used multiple permutations of automatically identified networks to compute RAI as reported in the fMRI literature.

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Contributors

MM performed data preprocessing and analysis and wrote the first draft of the manuscript. HE defined the research question and gave feedback on data analysis and interpretation, revising the manuscript. RK supervised the data preprocessing and analysis and revised the manuscript. BM gave feedback on data analysis and revised the manuscript. JS prepared the lifetime substance use data, gave feedback on the data analysis, and revised the manuscript. TV provided the data and revised the manuscript. Tulsa 1000 Investigators were involved in conducting the original Tulsa 1000 study and gave feedback on the manuscript. MP supervised the project, gave feedback on data analysis and interpretation, and revised the manuscript.

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Results—First, the RAI as a metric depended substantially on the approach that was used to define the network components. Second, regardless of the selection of networks, after controlling for multiple testing there was no difference in RAI scores between SUD and HC. Third, the RAI was not associated with any substance use-related self-report measures.

Conclusion—Taken together, these findings do not provide evidence that RAI can be used as an fMRI-derived biomarker for the severity or diagnosis of individuals with SUD.

Keywords

resting-state fMRI; independent component analysis; resource allocation index; substance use disorder; biomarker; default mode network; executive control network; salience network

1. Introduction

Substance use disorder (SUD) is a major public health concern (Rehm & Shield, 2019) carrying a \$740 billion annual financial burden in 2017 (NIDA, 2017). It is characterized by compulsive drug-seeking, loss of control over drug intake, negative affect, and withdrawal (Volkow et al., 2016). Although standard approaches using screening drug concentrations and their metabolites are highly reliable, these tools reflect relatively recent drug use and have limited utility for diagnosis and severity monitoring. New approaches are required to evaluate chronic drug exposure and shed light on neurobiological mechanisms involving positive and negative reinforcement processes contributing to SUD (Koob, 2015; Paulus, 2020). Neuroimaging modalities have shown promise in highlighting brain mechanisms involved in the transition from drug experimentation to drug addiction (Ekhtiari et al., 2016; Volkow et al., 2015) and can be employed to predict and track clinical SUD outcomes including relapse and treatment adherence (Moeller & Paulus, 2018).

Blood-oxygen level dependent (BOLD) signals acquired from the cortex while individuals are scanned at “rest” show reproducible patterns (Biswal et al., 1995) that are the basis for resting-state functional magnetic resonance imaging (rsfMRI). These patterns reflect the correlated, spontaneous nature of signal fluctuations in specific brain regions known as resting-state networks (RSNs) that are affiliated with many well-studied brain systems (Biswal et al., 1995; Biswal, 2012; Power, 2020). Functional Connectivity (FC) is a statistical dependency (i.e. temporal correlation) between different brain regions based on electro/neuro-physiological signals (Bijsterbosch et al., 2017). Pearson’s correlation coefficient is commonly used to quantify FC strength (Bijsterbosch et al., 2017; Power, 2020). Three major RSNs implicated in some psychiatric disorders include the default mode network (DMN), executive control network (ECN) and the salience network (SN) (Menon, 2011). First, DMN is comprised of multiple sub-networks that include posterior cingulate cortex, medial prefrontal cortex, and medial temporal lobe, activated in response to self-referencing thoughts and internal information processing (e.g., autobiographical, semantic, and episodic memory, value-based decision making, and emotion regulation) (Buckner & DiNicola, 2019; Di & Biswal, 2014; Long et al., 2008). Second, ECN includes dorsolateral prefrontal cortex and lateral posterior parietal cortex, focusing on information processing (e.g., working memory, rule-based problem solving and decision making) (Markett et al., 2014; Seeley et al., 2007; Sridharan et al., 2008). Third, SN comprises dorsal anterior

cingulate cortex, fronto-insular cortex, amygdala, and the union of the substantia nigra/ventral tegmental area, and is involved in: (a) distinguishing motivationally relevant events in the environment; (b) filtering out “irrelevant” stimuli (Seeley et al., 2007); and (c) initiating responses to prioritized events by allocating resources to engage DMN or ECN (Chong et al., 2017; Menon, 2015; Menon & Uddin, 2010). There is preliminary evidence that the FC between these three RSNs might be aberrant among individuals with SUD (Fedota et al., 2018; Pariyadath et al., 2016; Sutherland et al., 2012) and may be involved in maintaining the cycle of addictive behaviors (Volkow et al., 2015). A triple network model of psychopathology (Menon, 2011) has advocated the calculation of a resource allocation index (RAI) to evaluate the degree of SN-DMN and SN-ECN dysfunction (Choi et al., 2013; Lerman et al., 2014; Reese et al., 2019; Zhang et al., 2017). The RAI is calculated as a difference score between SN-ECN FC and SN-DMN FC, with more positive scores reflecting a stronger SN bond with ECN as opposed to DMN (Lerman et al., 2014).

Several investigators have used rsfMRI to examine RAI in individuals with SUD. Specifically, lower RAI scores reflecting stronger SN-DMN as opposed to SN-ECN FC appear to: (a) characterize nicotine smokers during abstinence as opposed to active use (Lerman et al., 2014); (b) signal higher craving in individuals with internet gaming disorder (Zhang et al., 2017); and (c) show an increase in the likelihood of cocaine users disengaging from a distress tolerance task (Reese et al., 2019). On the whole, RSN studies of addiction use varying RAI calculations and tend to focus on one specific substance; this research approach can be contrasted with a transdiagnostic approach to SUD, which are often comorbid with mood/anxiety disorders and present within the context of polysubstance use (Filbey et al., 2018; Vergara et al., 2017; Zhang & Volkow, 2019). To further evaluate the utility of the RAI as a biomarker of SUD, extant RAI findings warrant replication across externally valid SUD samples presenting with heterogeneity in substance use comorbidity as well as mood/anxiety disorder co-occurrence. This is the first study to identify whether the RAI can differentiate individuals with lifetime opioid and/or stimulant (amphetamine and cocaine) use disorders from healthy adults, evaluating the utility of various RAI extraction methods reported in the literature (Choi et al., 2013; Lerman et al., 2014; Reese et al., 2019; Zhang et al., 2017). We hypothesized that: (1) SUD would exhibit lower RAI scores than healthy controls (HC); and (2) lower RAI scores would be associated with greater SUD symptom severity as well as lower abstinence duration.

2. Material and Methods

2.1. Participants

A subset of the first 500 participants of the Tulsa 1000 cohort (Victor et al., 2018), conducted at Laureate Institute for Brain Research (LIBR), Tulsa, OK were selected for rsfMRI analysis. Fig. 1 illustrates that total of 205 participants consisting of 58 HC and 147 SUD with stimulant and/or opioid use disorders ranging from 4 to 365 days of abstinence were included (all were abstinent at the time of scan, confirmed with a urine drug test). Ethical approval was obtained from Western Institutional Review Board and all research was carried out in accordance with the Declaration of Helsinki. All participants provided written informed consent and received compensation for their participation (Victor et al., 2018).

Participants were included in analyses if they were HCs (no DSM-IV or DSM-5 diagnosis) or qualified for SUD, meeting DSM-IV (APA, 1994) or DSM-5 (APA, 2013) criteria for a stimulant (amphetamine, cocaine) and/or opioid use disorder. Clinical symptoms were assessed by means of the Mini International Neuropsychiatric Interview (MINI V.6.0 and MINI V.7.0) (Lecrubier et al., 1997; Sheehan et al., 1997; Sheehan et al., 1998) diagnostic interviews that evaluated symptoms of SUD, panic disorder, social anxiety disorder, posttraumatic stress disorder, generalized anxiety disorder, eating disorder, bipolar disorder, obsessive-compulsive disorder and major depressive disorder (Victor et al., 2018).

After data preprocessing, two HCs and 8 SUDs were excluded due to incomplete data or excessive head motion (mean framewise displacement > 0.25 mm, see Fig. 1). Group demographics and symptom information are presented in Table 1. Furthermore, lifetime DSM-IV disorders within the SUD group ($N = 139$) are provided in Table 2.

2.2. Image Acquisition

Two sets of imaging data including T1-weighted structural and rsfMRI images (8 min scans) were collected using two identical GE Discovery MR750 3T scanners with 8-channel head coils and acquisition parameters [2000ms TR, 27ms as TE and FOV/slice=240/2.9mm, 128×128 matrix, 39 axial slices, 240 repetitions]. Participants were instructed to keep their eyes open and fixated on a crosshair during scanning (Victor et al., 2018).

2.3. fMRI Preprocessing and Analysis Pipeline

Both the raw structural and functional data were converted to NIfTI format using AFNI *3dcalc* (Cox, 1996). We followed the rsfMRI preprocessing protocol established by the UK Biobank cohort, depicted in Fig. 2 (Alfaro-Almagro et al., 2018; Miller et al., 2016), conducted in FSL (FMRIB Analysis Group, Oxford University) (Jenkinson et al., 2012; Smith et al., 2004; Woolrich et al., 2009).

Independent component analysis (ICA) (Comon & Jutten, 2010) is the conventional approach to decompose the spatio-temporal fMRI BOLD signal into independent components (ICs) that reflect coordinated activity of large-scale neural networks (Bijsterbosch et al., 2017; Calhoun et al., 2009; Moradi et al., 2020; Smith et al., 2013). A motivation for using ICA is that studies deriving their regions of interest (ROI) from the dataset (as opposed to general ROI atlases) have the best outcomes in terms of accuracy and replicability (Smith et al., 2011).

Each participant's data were extracted using FSL's Brain Extraction Tool (Smith, 2002) and the first 4 volumes from each functional dataset were removed (to account for scanner saturation effects). High pass temporal filtering was performed with a cutoff of 0.01 Hz (Bijsterbosch et al., 2017). Slice timing correction, motion correction using MCFLIRT (Jenkinson et al., 2002), and Gaussian spatial smoothing with 5 mm full width at half maximum were also applied in order to ameliorate the influence of noise on the analysis. Furthermore, spatial normalization (registration) to Montreal Neurological Institute (MNI) 152 T1 2mm³ standard space was performed with non-linear registration and 12 degrees of freedom using FSL FNIRT (Andersson et al., 2007; Jenkinson et al., 2012; Smith et al., 2004; Woolrich et al., 2009).

Using FSL's MELODIC (Multivariate Exploratory Linear Optimized Decomposition into Independent Components) (Beckmann et al., 2005; Beckmann & Smith, 2004; Beckmann & Smith, 2005) we employed ICA to de-noise rsfMRI data at the individual subject level (SICA) (Bijsterbosch et al., 2017; Griffanti et al., 2017; Salimi-Khorshidi et al., 2014) with an unconstrained number of ICs to detect and remove artifacts from the dataset. Those noise/artefactual components were regressed out of the dataset by a semi-automated procedure using FSL FIX (Griffanti et al., 2014; Salimi-Khorshidi et al., 2014). FSL FIX utilizes machine learning approaches for signal/noise IC classification and needs to be trained on a subset of data to correctly classify the ICs resulting from SICA into signal or noise (Bijsterbosch et al., 2017; Griffanti et al., 2017). In order to apply FIX, a user must select a training set and threshold. This selection was made by applying all six available training sets in FIX with varying thresholds to a subset of our data. We compared manual classification of the ICs following the guidelines specified in (Griffanti et al., 2017) to the results of each training set and threshold combination and determined the Standard training set with a threshold of 20 had the best outcomes in our data. Therefore, the whole dataset was cleaned up using these settings. Independence of the training set from the test set was maintained by following this approach (Scheinost et al., 2019).

On average across all subjects, SICA decomposed each rsfMRI image into 65 ICs (consisting 18 noise ICs). FIX results were visually inspected to ensure the quality of final cleaned data.

2.4. Network Identification and Group Network Extraction

The resulting cleaned datasets were used for group-level ICA (GICA) using a temporal concatenation approach. GICA was performed using an identical ICA tool/algorithm used in prior research (Choi et al., 2013; Lerman et al., 2014; Reese et al., 2019; Zhang et al., 2017) (FSL MELODIC) with the model order of 30 ($d = 30$); detected ICs were compatible to those reported in earlier works (Smith et al., 2009). For network labeling and identification, we utilized a semi-automatic approach (Reineberg et al., 2015) consisting of correlating the whole set of GICA ICs with four different published RSN reference atlases (Laird et al., 2011; Shirer et al., 2012; Smith et al., 2009; Yeo et al., 2011) and the label for each signal IC (RSN) was determined. Two experienced experts at LIBR (MP and HE) were consulted to visually inspect the network labels and check the accuracy of network label selection procedure. From 30 GICA ICs, four ICs were detected as noise/artefactual and 26 ICs were signals. Using a dual regression method (Beckmann et al., 2009; Nickerson et al., 2017), the ICs from GICA were mapped onto each participant's functional data to extract subject-specific timeseries and spatial maps of corresponding RSNs, which were then used for further analyses, including the computation of RAI scores for each participant.

2.5. RAI Computations

The RAI is defined as the difference of the correlation coefficients between SN-ECN and SN-DMN pairs for each participant (Choi et al., 2013; Lerman et al., 2014; Reese et al., 2019; Zhang et al., 2017)

$$RAI = f(CC_{SN, ECN}) - f(CC_{SN, DMN}), \quad (1)$$

where $CC_{a,b}$ is Pearson's correlation coefficient between timeseries of any given two networks of a and b and $f(x)$ is Fisher's z-transformation of CC , as in

$$f(CC) = \frac{1}{2} \times \ln\left(\frac{1 + CC}{1 - CC}\right), \quad (2)$$

since this transformation is applied in FC analyses to transform correlation coefficients into an approximately normal distribution (Scheinost et al., 2019). The RAI is positive if the connectivity between SN and ECN is larger than the connectivity between SN and DMN, i.e. the SN is more aligned with ECN, presumably aiding to adjust the individual to engage in processing that is adaptive to the environment.

Running GICA with any given model order can yield a number of signal and noise/artefact ICs. It is common that more than one IC would be identified as DMN, ECN or SN (Moradi et al., 2020) and any of them could be used to calculate the RAI. We computed the RAI in an all-inclusive scenario in order to achieve following objectives:

1. to test for the expected group (SUD versus HC) effect on the RAI, and
2. to illustrate the possible subjectivity that IC selection has on RAI computations.

Previous studies have employed “composite” measures of multiple ICs as indices of DMN, SN or ECN. For example, they have merged spatial maps of every IC matching DMN together to create one composite map of DMN. A similar approach was used for SN and ECN and an extension was proposed using left and right ECN for lateralized versions of RAI (Choi et al., 2013; Lerman et al., 2014; Reese et al., 2019; Zhang et al., 2017). In order to be consistent with published RAI studies, we also computed RAI using the composite and lateralized methods. Furthermore, prior studies have performed GICA with a different model order (range: 20–28 ICs), less than our original 30 ICs. Hence, we repeated GICA at four different deposition levels ($d = 15, 20, 25, 35$) as well and computed composite RAIs based on these metrics, to make sure that we have not moved further away from the composite measures previously employed in the literature. Together, RAI was computed in 31 different ways for each subject (24 methods using different combinations of ICs detected by GICA at $d = 30$, as well as one composite method of these ICs and also lateralized left and right RAI, plus composite indices from running GICA at 15, 20, 25 and 35 model orders). For RAI calculations, each participant's timeseries was imported into R software (Version 3.6.1) (Dessau & Pipper, 2008) and the corresponding timeseries of the SN, DMN and ECN (ICs corresponding to these three networks) were used to compute the RAI.

2.6. Group Level Statistics

2.6.1. RAI Variability—To quantify the degree of heterogeneity among different RAI formulations, we computed Pearson correlations between all possible RAI pairs. If these correlations are all large, it would be evidence that different IC combinations measure roughly the same construct. On the other hand, if pairs of RAI scores are weakly or unrelated to one another, it would be evidence that they are not measuring the same

underlying construct. In order to visualize the results, we used the *corrplot* function from *corrplot* package version 0.84 (Wei et al., 2017) in R.

2.6.2. Group Tests and Effect Sizes—We compared group differences by applying a two-sample *t*-test (*t.test* function from *stats* package version 4.0.0 in R). Furthermore, we measured the effect size magnitude of group differences in the RAI (Cohen's *d*) (Cohen, 2013) for all formulations of RAI using the *cohen.d* function from the *effsize* package version 0.7.6 (Torchiano, 2019) in R.

2.6.3. Group Linear Models—To investigate the effect of abstinence duration and other variables of interest on the RAI among SUD, we applied linear modeling (James et al., 2013), with each RAI score as the dependent variable and the following as independent (predictor) variables: medication status (0 versus 1), drug of choice (in five categories of: no specific drug as 0, opiates as 1, stimulants as 2, sedatives as 3, and marijuana as 4), stimulant use status and opioid use status (0 versus 1; as subgroups of SUD and their interaction term), abstinence duration (days), head motion, age (years), sex (0 versus 1), education, the Drug Abuse Screening Test (DAST-10) score (Bohn et al., 1991), Patient Health Questionnaire-9 (PHQ-9) score (Kroenke & Spitzer, 2002) and the Overall Anxiety Severity and Impairment Scale (OASIS) score (Campbell-Sills et al., 2009) as formulized in

$$\begin{aligned} RAI \sim & \text{Abstinence Duration} + \text{Head Motion} + \text{Age} + \text{Sex} + \text{Education} \\ & + \text{Medication status} + \\ & \text{Drug of choice} + \text{PHQ} + \text{OASIS} + \text{DAST} + \text{Stimulant use status} \times \text{Opioid} \\ & \text{use status} . \end{aligned} \quad (3)$$

This analysis was performed using the *lm* function from the *stats* package version 4.0.0 in R. This model was fitted to all RAI constructs. To visualize different model comparisons, we used the *ggplot2* package version 3.2.1 (Wickham, 2011) and the *metaviz* package version 0.3.0 (Kossmeier et al., 2017) in R.

3. Results

3.1. Group Network Extraction and RAI Computations

Based on GICA results, seven ICs pertained to RAI computations; there were two ICs within SN (including anterior insula, posterior insula and anterior cingulate cortex) (Chong et al., 2017; Menon, 2015; Menon & Uddin, 2010), two ICs within ECN (lateralized as left and right fronto-parietal cortex) (Markett et al., 2014; Seeley et al., 2007; Sridharan et al., 2008) and three ICs within DMN (including precuneus, medial prefrontal cortex, subcallosal cortex, orbitofrontal cortex and anterior cingulate cortex) (Buckner & DiNicola, 2019). Compared to the GICA outcomes reported in earlier works utilizing an RAI and ICA approach, our set of ICs encompass all RSNs used for all RAI calculations reported in (Choi et al., 2013; Lerman et al., 2014; Reese et al., 2019; Zhang et al., 2017). A total of 24 possible combinations of these ICs were then input into the RAI formula (Fig. 3) for each participant.

Composite maps of these ICs were also created for DMN, SN and ECN, and lateralized versions of the RAI were computed. Also, composite maps of these networks were built

using GICA results at four different ICA model orders in addition to the original 30 IC decomposition. In total, 31 approaches were used to compute RAI scores for each subject.

3.2. Construct Validity of RAI: Single versus Multiple Constructs

Although there are strong correlations among *some* RAI measures (Fig. 4), the RAI scores vary widely in their covariation. The correlation among RAI scores varied from -0.52 to 0.83 with a mean correlation of 0.14 . Thus, there is considerable heterogeneity among RAI formulations.

Performing k-means clustering using an average silhouette width method for k estimation revealed the presence of at least four distinct clusters, as illustrated by the cluster plot Fig.5a and hierarchical clustering in Fig.5b, demonstrating that not all RAIs are measuring the same construct.

3.3. Group Analyses

None of the RAI measures showed a statistically significant difference between SUD and HC based on independent samples t-tests (see Tables S1 and S2). The 95% confidence interval for each RAI effect size was consistent with a zero-level Cohen's d effect size (Fig. 6), demonstrating that reliable differences between HC and SUD were not observed.

The effect size of the difference in RAI scores between HC and SUD varied from -0.26 to 0.21 with a mean + SEM of -0.005 . Furthermore, there were not any significant differences observed between RAI measures among SUD subgroups (stimulant users, opioid users and both) and HCs (see Figs. S1-S6).

3.4. Linear Modeling Results

For each RAI measure as the outcome variable, we constructed a multivariate model (Eq. 3) that included multiple predictors including abstinence duration, DAST-10 score, and SUD subgroup, as well as other demographic, personality, and clinical symptom variables (Fig. 7). A few of the RAIs showed a significant effect for DAST-10, yet after false discovery rate (FDR) p-value correction, none were less than 0.05 .

4. Discussion

This study examined whether RAI scores, quantified as the difference between SN-ECN and SN-DMN RSNs (Choi et al., 2013; Lerman et al., 2014; Reese et al., 2019; Zhang et al., 2017), could be used as diagnostic and/or severity biomarkers, i.e. would be able to robustly distinguish between SUD and HC or would correlate with self-reported measures of substance use severity. More specifically, we hypothesized that SUD would exhibit lower RAI scores than HC, reflecting lower SN connectivity with ECN than DMN, which may explain decision-making impairments experienced by SUD. Moreover, we predicted that within SUD, lower RAI scores would be associated with greater addiction symptom severity and more recent illicit substance use. Using GICA to detect RSNs of interest (ICs:2 SNs, 3 DMNs and 2 ECNs) and dual regression for timeseries extraction, subject-specific RAI measures were computed in 24 possible combinations of these RSNs. In order to replicate

RAI calculation methods in previous studies, we utilized “composite” measures of multiple ICs as indices of DMN, SN or ECN and the lateralized formulations of these ICs. And besides the original ICs from running GICA with $d = 30$ model order, composite indices from performing GICA with 15, 20, 25 and 35 model orders were also included as part of our total 31 RAI computations per subject. Contrary to the hypotheses, our results indicated that SUD did not differ from HC on any of the 31 RAI metrics. In addition, the varying degree of correlation between the 31 RAI metrics within our sample suggests that the RAI as measured thus far in the literature is not a single, well-defined construct.

It has been argued that a “winner’s curse” is a common phenomenon in many follow-up studies (Ioannidis, 2008). There are several explanations why we did not replicate significant group differences between SUD and HC. First, the relatively larger sample size analyzed for this study (205 individuals) compared to previous studies (under 80 individuals) (Choi et al., 2013; Lerman et al., 2014; Zhang et al., 2017) may partially explain discrepancies in findings. Second, overfitting could lead to false positives in previous related works (Gillan & Whelan, 2017). Third, although our SUD sample is representative of the greater SUD population with respect to psychiatric comorbidity (Goldner et al., 2014; Lai et al., 2015), the inclusion of polysubstance users with lifetime mood and/or anxiety disorders could have introduced heterogeneity and complexity with respect to symptom presentation that impacted our results. Although we included current depression and anxiety symptom severity metrics (PHQ-9 and OASIS scores) in our within-SUD analyses, it may be necessary to evaluate other symptom classes that relate to the RAI or go beyond a three-network resting-state model to more accurately characterize these individuals. Finally, prior RAI SUD studies focused on specific substances like nicotine (Lerman et al., 2014) or cocaine (Reese et al., 2019), and therefore their findings may only be specific to these substances.

The present study possesses several advantages in extending the SUD RAI literature, including: (1) collecting rsfMRI data on a larger SUD sample than previous addiction studies; (2) focusing on individuals experiencing problems with stimulants and/or opioids, two drug classes linked to twin epidemics in the United States (Jones et al., 2020; Jones et al., 2019; Strickland et al., 2019); and (3) following an established data preprocessing and reliable analysis pipeline (Smith et al., 2013) in accordance with prior research. Considering the study limitations, SUD comorbidity with multiple psychiatric disorders might have an effect on brain function and therefore on addiction research outcomes (Dixon et al., 1991; Santucci, 2012; Wu & Blazer, 2013). Drug recency and abstinence duration are important factors to aid in interpreting our cross-sectional results; however, a longitudinal investigation focused on drug recency and abstinence duration could help to better explain these relationships.

5. Conclusions

The absence of novel neuroscience-based biomarkers for psychiatric symptoms is evident in the literature. An ideal biomarker should be quantifiable, reliable, replicable, connected to the pathophysiology of the illness, clinically meaningful and have the potential to differentiate between the groups under study. In addition, it would be helpful for a biomarker

to be correlated with changes in symptom severity with the ability to predict treatment outcomes. An adequate biomarker, or a biomarker for specific aspects of an illness (e.g. a diagnostic biomarker), should be able to accomplish a subset of these functions. The present study was unable to replicate attenuated RAI scores as a diagnostic marker for SUD in a sizable sample of individuals with stimulant and/or opioid use disorders. While the RAI did not show utility as a diagnostic biomarker, future studies should still investigate the RAI as a predictive or treatment response biomarker and find practical ways to identify biomarkers of addiction. Finally, future work should consider extending the existing triple network model to encompass other RSNs that might have a direct effect on the processing of salient events by SN in participants suffering from SUD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Conflict of Interest

MP is an advisor to Spring Care, Inc., a behavioral health startup; he has also received royalties for an article about methamphetamine in UpToDate.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Highlights

- Neuroscience-based biomarkers are lacking for substance use disorders (SUD).
- Resource allocation index (RAI) has yet to be extensively tested in SUD samples.
- RAI fell short to be a consistent biomarker for SUD.
- RAI was dependent on the approach that was used to define the network components.
- No difference in RAI scores between SUD and HC after controlling for multiple testing.

Figure 1.
Flow diagram for participant inclusion.

Figure 2.
Preprocessing and data analysis pipeline.

Figure 3.

Network identification from GICA results with 30 component decomposition (model order), within a triple network model framework. SN = salience network. DMN = default mode network. ECN = executive control network. IC = independent component. RAI = resource allocation index.

Figure 4.

Correlation of all RAI measures across participants. RAIs 1 to 24 are computed based on 24 combinations of ICs from GICA 30 decomposition shown in Fig.3, and “Composite”, IRAI and rRAI (lateralized) were calculated by merging those ICs, according to the previous studies. RAIs GICA 15 to 35 are also composite RAIs, except they are created using maps from running GICA with 15, 20, 25 and 35 model orders accordingly.

Figure 5. Cluster plot (a) and hierarchical clustering (b) of RAI measures across participants. These plots are based on performing k-means clustering ($k = 4$), using average silhouette method to estimate k .

Combination	Healthy Controls	Substance Users	Magnitude
ECN1-SN1.SN1-DMN1	0.165	0.198	-0.106
-DMN2	0.125	0.128	-0.01
-DMN3	-0.096	-0.061	-0.128
ECN1-SN1.SN2-DMN1	-0.187	-0.257	0.197
-DMN2	-0.048	-0.036	-0.033
-DMN3	0.139	0.115	0.084
ECN2-SN1.SN1-DMN1	0.227	0.301	-0.234
-DMN2	0.187	0.231	-0.161
-DMN3	-0.034	0.042	-0.258
ECN1-SN2.SN2-DMN1	0.282	0.231	0.158
-DMN2	0.422	0.452	-0.086
-DMN3	0.609	0.604	0.016
ECN2-SN2.SN2-DMN1	0.173	0.107	0.209
-DMN2	0.313	0.328	-0.035
-DMN3	0.5	0.479	0.058
ECN2-SN1.SN2-DMN1	-0.126	-0.154	0.074
-DMN2	0.014	0.067	-0.169
-DMN3	0.201	0.219	-0.067
ECN1-SN2.SN1-DMN1	0.635	0.687	-0.175
-DMN2	0.595	0.617	-0.082
-DMN3	0.374	0.428	-0.175
ECN2-SN2.SN1-DMN1	0.526	0.562	-0.12
-DMN2	0.486	0.492	-0.023
-DMN3	0.265	0.303	-0.108
Composite: ECN-SN-DMN	0.36	0.377	-0.075
Left_EC_N-SN-DMN	0.337	0.37	-0.139
Right_EC_N-SN-DMN	0.453	0.415	0.167
ECN-SN-DMN - GICA 15	0.511	0.493	0.066
- GICA 20	0.192	0.144	0.213
- GICA 25	0.274	0.242	0.127
- GICA 35	0.199	0.221	-0.091

Figure 6.

RAI group difference results from 24 possible combinations of SN, ECN and DMN components (95% confidence interval) with effect size magnitude represented by Cohen's *d*. Also, group differences based on composite indices of ECN, SN and DMN, and lateralized RAIs are shown. Last four rows depict group difference based on composite maps created from running GICA with four different model orders besides the original 30 component decomposition.

Figure 7.

Manhattan plot illustrating 31 RAI linear model fitting results on various variables with their estimates and corresponding p -values.

Table 1.

Participant information and demographics.

	HC (n=56)	SUD (n=139)
Age		
Mean (SD) [†]	32.1 (11.3)	33.5 (8.71)
Median [Min, Max]	28.0 [18.5, 53.8]	31.8 [19.2, 55.4]
Sex		
Female	29 (51.8%)	76 (54.7%)
Male	27 (48.2%)	63 (45.3%)
Head Motion		
Mean (SD)	0.0842 (0.0422)	0.100 (0.0497)
Median [Min, Max]	0.0752 [0.0255, 0.242]	0.0860 [0.0334, 0.250]
Education		
Less than seven years of school	0 (0%)	30 (21.6%)
Less than High School graduate	0 (0%)	2 (1.4%)
High School graduate (or completed equivalency)	8 (14.3%)	45 (32.4%)
Completed some college/technical school or Associate's degree	27 (48.2%)	56 (40.3%)
College graduate	15 (26.8%)	6 (4.3%)
Graduate professional training (Master's or above)	6 (10.7%)	0 (0%)
DAST-10[‡]*		
Mean (SD)	0.107 (0.366)	7.83 (1.79)
Median [Min, Max]	0.00 [0.00, 2.00]	8.00 [2.00, 10.0]
Abstinence Duration		
Mean (SD)	NA (NA)	108 (81.4)
Median [Min, Max]	NA [NA, NA]	90.0 [4.00, 365]
Missing	56 (100%)	0 (0%)
OASIS[§]		
Mean (SD)	1.14 (1.39)	5.47 (4.58)
Median [Min, Max]	1.00 [0.00, 5.00]	5.00 [0.00, 17.0]
PHQ-9[¶]		
Mean (SD)	0.804 (1.20)	5.95 (5.41)
Median [Min, Max]	0.00 [0.00, 5.00]	5.00 [0.00, 23.0]
Missing	0 (0%)	1 (0.7%)

[†]SD: Standard Deviation[‡]DAST-10: Drug Abuse Screening Test 10[§]OASIS: Overall Anxiety Severity and Impairment Scale[¶]PHQ-9: Patient Health Questionnaire-9

* Healthy Controls had low cut-off DAST-10 scores.

** HC: Healthy Control, SUD: Substance Use Disorder

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Table 2.Lifetime DSM-IV Disorders within the SUD group ($N=139$).

Substance Dependence	Number	Percent
Stimulant (Cocaine and/or Amphetamine)	94	68%
Opioid	50	36%
Alcohol	41	29%
Cannabis	37	27%
Sedative	31	22%
None (only Substance Abuse)	8	6%
Hallucinogen	2	1%
Polysubstance *	4	3%
Mood Disorders	Number	Percent
Major Depressive Disorder	64	46%
Bipolar Disorder	2	1%
Anxiety Disorders	Number	Percent
Generalized Anxiety Disorder	22	16%
Posttraumatic Stress Disorder	20	14%
Panic Disorder	15	11%
Social Phobia	14	10%
Eating Disorders	Number	Percent
Bulimia Nervosa	1	<1%

Note.

* Designated only when individual substance dependence diagnoses were not individually recorded.