Evidence accumulation and associated error-related brain activity as computationally informed prospective predictors of substance use in emerging adulthood

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Abstract

Substance use peaks during the developmental period known as emerging adulthood (roughly ages 18–25), but not every individual who uses substances during this period engages in frequent or problematic use. Previous studies have suggested that individual differences in neurocognition may prospectively predict problematic substance use, but mechanistic neurocognitive risk factors with clear links to both behavior and neural circuitry have not yet been identified. Here we take an approach rooted in computational psychiatry, an emerging field in which formal models of neurocognition are used to identify candidate biobehavioral dimensions that confer risk for psychopathology. Specifically, we test whether lower efficiency of evidence accumulation (EEA), a computationally tractable process that drives neurocognitive performance across many tasks, is a risk factor for substance use in emerging adults. In an fMRI substudy within a sociobehavioral longitudinal study (n=106), we find that lower EEA and reductions in a robust neural-level correlate of EEA (error-related activations in salience network and parietal structures) measured at ages 18–21 are both prospectively related to higher levels of substance use during ages 22–26, even after adjusting for other well-known risk factors. Results from Bayesian model comparisons corroborated inferences from conventional hypothesis testing and provided evidence that both EEA and its neural correlates contain unique predictive information about substance use involvement. Overall, these findings suggest that EEA is a mechanistic, computationally tractable neurocognitive risk factor for substance use at a critical developmental period, with clear links to both neural correlates and well-established formal theories of brain function.

Keywords: computational psychiatry, diffusion model, drift rate, salience network, addiction

Introduction

Problematic substance use, which affects tens of millions of Americans, can have devastating consequences, including substantial physical, emotional, and financial burden. Drug overdose deaths topped 70,000 in the US in 2017 alone[1], and the annual economic cost of substance abuse has been estimated at over $740 billion[2–5]. However, not everyone who tries alcohol, tobacco, or other drugs goes on to develop a substance use disorder (SUD; see Table 1 for abbreviations used in this article). A better understanding of the mechanisms that underlie problematic substance use risk is essential for improving prevention and treatment efforts.

Substance use increases throughout adolescence and peaks during a period characterized as "emerging adulthood" (ages 18–25)[6]. According to an ongoing national survey on US substance use, rates of past-month marijuana use were highest at ages 21–22 (27.5%), and past-month alcohol use was highest at ages 23–24 (75.1%)[7]. Although substance use is relatively common in this developmental period, frequent use confers both short- and long-term risks to mental and physical health[8]. In addition to changing social roles and contexts that increase exposure to drugs and alcohol during adolescence and emerging adulthood, neurodevelopmental changes during this time may relate to use patterns. The brain continues to mature throughout youth into the mid-20s, specifically in circuitry involved in cognitive control, and immaturity in this circuitry is theorized to contribute to substance use and other risk-taking behaviors[9].

Indeed, researchers have found evidence that behavioral and neural measures of controlled cognitive processes predict substance use behaviors during this developmental period. For instance, poor behavioral performance and abnormalities in neural responses during working memory tasks have been associated with increased substance use risk in adolescence[10–13]. Inhibitory control deficits, typically probed with the go/no-go or stop signal paradigms, are also

thought to contribute to risk. Meta-analytic studies have found poorer behavioral performance on these tasks across a variety of substance use disorders[14]. Prospective neuroimaging work has found that reduced activation in the prefrontal cortex during inhibitory errors predicts problem use in early adolescence[15], suggesting that neural responses associated with error monitoring may be particularly relevant to links between cognitive processes and risk for use.

Although these studies suggest that individual differences in neurocognition predict problematic substance use at critical developmental periods, they have exclusively focused on neurocognitive constructs derived from earlier factor analytic work (e.g., working memory, inhibition[16]). Such a focus is problematic because these cognitive ontologies have recently been found to display questionable replicability[17,18], and because constructs defined mainly based on behavioral test score covariation, rather than on an understanding of the mechanistic processes involved in cognition, are likely to display ambiguous links to neural circuitry[19]. Computational psychiatry, an emerging field in which biologically plausible formal models are used to describe performance on clinically relevant tasks[19], offers a promising alternative framework. This approach aims to identify candidate biobehavioral dimensions that confer risk for psychopathology by focusing on formal model parameters that index mechanistic processes underlying task behavior and their neural correlates.

Sequential sampling models[20] suggest at least one such dimension that may predict substance use risk. These models explain behavior on choice response time (RT) tasks (a category that subsumes most current “cognitive control” tasks) as the result of a process in which individuals gradually gather noisy evidence from the environment for each possible choice until a critical evidence threshold for one choice is reached. Crucially, the mechanistic processes posited by these models align remarkably well with neurophysiological data[20,21]. The diffusion

decision model (DDM)[22], one of the most commonly used sequential sampling models, frames the choice process as a decision variable that drifts over time, in a pattern influenced by stochastic evidence accumulated from the stimulus, between two boundaries representing each possible choice (Figure 1). When the process terminates at one of these boundaries (e.g., the "go" boundary in a go/no-go task), the corresponding response occurs. Although the DDM features several main parameters (detailed in Figure 1), the "drift rate" (*v*) parameter, which determines the rate at which the decision variable drifts toward the boundary for the correct choice, is often of key interest. In experimental work, drift rates are typically used to index the quality of evidence that can be extracted from a stimulus[22]. For example, stimuli that provide more ambiguous information about which choice is correct, or other conditions that make decisions more difficult, lead to relatively slower drift rates (reflecting poorer evidence quality).

When considered as an individual differences dimension, drift rate from the DDM indexes the efficiency with which individuals can gather relevant evidence to make an accurate choice in the context of background noise (efficiency of evidence accumulation: EEA). Measures of EEA display clear trait-like properties[23], and lower levels of EEA have been repeatedly linked to externalizing psychopathologies comorbid with substance use[24,25]. Furthermore, EEA may underlie individual differences in performance of working memory and response inhibition tasks[26–28], suggesting EEA could explain previously identified prospective links between features of both types of tasks and substance use.

We recently found[29] that EEA on a go/no-go task (measured across both "go" and "no-go" trials) was strongly related to the inhibitory performance (false alarm rate) of young adults (18–21) and was robustly positively correlated with error-related activation in the anterior cingulate cortex (ACC) and anterior insula. Both regions are considered key hubs of the salience

network[30], a brain network involved in triggering cognitive control in response to errors and other salient events. Hence, when considered with earlier evidence that reduced neural responses to errors are prospectively linked to substance use in youth[15], this work suggests that EEA could provide a computationally informed explanation of how salience network functioning relates to both performance on current probes of cognitive control and associated clinical outcomes.

Taken together, these prior findings suggest EEA could index a mechanistic biobehavioral dimension with clear links to both neural-level correlates and well-established mathematical theories of brain function, and that lower levels on this dimension could confer risk for substance use. In the current study, we build on our prior work[29] to explicitly test whether EEA and its neural correlates (error-related activations) prospectively relate to individuals' degree of substance use in emerging adulthood. We use an approach that leverages both traditional frequentist hypothesis testing and Bayesian model comparison to quantify the strength and robustness of evidence for these prospective relationships. As recent findings have indicated that neural activity related to cognitive states and behavioral covariates is typically distributed across large brain networks, rather than being exclusively associated with discrete regions[31,32], we also leverage a multivariate network-based measure of error-related activation.

We tested two main hypotheses: 1) on the basis of our previous work[29], we expected that EEA measured on a behavioral task would display a robust, positive relationship with a summary neural measure of error-related activation, and 2) we predicted that both EEA and this error-related activation measure would display negative relationships with prospective substance use. In addition to these specific hypotheses, we also sought to evaluate whether EEA and its neural-level correlates provide unique (versus redundant) predictive information about use. Although we did not have a strong a priori expectation about whether this would be the case, we presumed

that, as EEA and its neural correlates are likely subject to method-specific variance from their respective measurement domains, it is plausible that both may contribute unique information.

Methods

Participants

Participants were volunteers for a functional magnetic resonance imaging (fMRI) substudy that was part of the Michigan Longitudinal Study (MLS)[33,34], a prospective study that has followed a sample of youth from families with history of alcohol use disorder (AUD) and youth from low-risk families who lived in the same neighborhoods. MLS assessments began at ages 3–5 and were continued through participants' late 20s and early 30s. Participants were excluded from the larger MLS if they displayed evidence of fetal alcohol syndrome and from the neuroimaging substudy if they: 1) had contraindications to MRI, 2) were left-handed, 3) had a neurological, acute, or chronic medical illness, 4) had a history of psychosis or first-degree relative with psychosis, or 5) were prescribed psychoactive medications, except psychostimulants prescribed for attention difficulties. Participants taking psychostimulants were asked to abstain from taking their medication for at least 48 hours prior to MRI scanning. Study procedures were carried out in accordance with the Declaration of Helsinki, and informed consent was obtained from all participants. MLS data are not currently publicly available, but can be accessed upon request.

For the current study, we examined a subset of participants who were included in our previous investigation of DDM parameters' neural correlates from common go/no-go neuroimaging contrasts (N=143)[29]. Individuals in this sample met all inclusion criteria outlined above and also had go/no-go behavioral and neuroimaging data available from their baseline scanning session (conducted at ages 18–21) that met quality control criteria for DDM fitting and

fMRI analysis (described in more detail in:[29]). Of this sample, a subset of individuals (*n*=106; 74%) had substance use outcome data from at least one time point between ages 22 and 26. To optimize our ability to identify reliable metrics of error-related activation and link them to EEA, we used data from the *full sample* (*N*=143) for dimension reduction of fMRI data and assessment of whether our summary measure of error-related activation was related to drift rate. We then used data from the *longitudinal subsample* (*n*=106) to evaluate prospective relationships with substance use. Demographics and summary statistics of relevant variables for the full sample and longitudinal subsample are displayed in Table 2.

Descriptions of the go/no-go task completed by participants, fMRI scanning parameters, and the fMRI pre-processing and single-subject analysis steps used in this and the previous study[29] are provided in Supplemental Materials.

EEA Measure

As detailed in our prior study[29], DDM parameters were estimated following methods established in a previous extension of the DDM to the go/no-go task[26,35] using functions from the R package *rtdists*[36]. To enhance parameter recovery, we fit a simplified version of the DDM that included only the following parameters (which are described in more detail in Figure 1): drift rates for go (respond) and no-go (inhibit) trials (*v.go*, *v.nogo*), starting point (*z*), boundary separation (*a*), and non-decision time (*Ter*). For the current study, we used parameter estimates obtained in this previous model fit, with the average of drift rates across go and no-go trials (*v.avg*) as the primary index of EEA.

Error-related Neural Activity Measure

We included regions of interest (ROIs) from our previous study[29], obtained by conducting a term-based meta-analysis in Neurosynth[37] with the term “error”. We downloaded

the "association test" statistical map from this meta-analysis, which indicates whether activation in each voxel occurs more consistently in studies that mention the term "error" than in those that do not (see: neurosynth.org/faq). We excluded clusters with <10 voxels from this map (*n*=14 clusters between 2 and 6 voxels; *n*=32 individual/isolated voxels) and then, for the 8 clusters that remained (minimum size = 28 voxels), centered 8mm radius spheres about their peak coordinates (Table 3; Figure 2a). Regions included ACC and two clusters spanning bilateral insula and nearby inferior frontal gyrus (IFG).

We next extracted average parameter estimates from the primary "error monitoring" contrast of interest (failed inhibitions on "no-go" trials > "go" responses) within each ROI, and entered these estimates into a principal component analysis (PCA) using the R package *FactoMineR*[38]. We used scores of the first component (PC1) from this PCA as our primary measure of error-related activation, in order to harness the aforementioned advantages of a network-based approach, and anticipated that this component would display strong loadings from the ROIs closely associated with the salience network in previous literature (ACC and bilateral insula/IFG)[30]. However, for comprehensiveness, we also report prospective relationships between neural activations from discrete brain regions and substance use in Supplemental Materials. Furthermore, as results of the PCA also revealed a second component (PC2) that was of potential interest because of its links to striatal activation (see below), associations between this component and substance use were also assessed in our primary analyses.

Substance Use Measures and Covariates

Substance use was assessed annually in the MLS sample with the Drinking and Drug History Form[39]. We aimed to create an outcome measure that indexed the degree to which individuals used the three most common substances of abuse — alcohol, marijuana and tobacco

— during emerging adulthood, and therefore focused on three measures from this questionnaire: drink volume (number of alcoholic drinks in the past year), marijuana frequency (number of days in the past year when marijuana was used), and cigarette frequency (number of days in the past year when cigarettes were used). To obtain a stable measure of how frequently individuals used these substances during ages 22–26, participants' responses for all ages with available data during this period were averaged for each substance (mean number of time points per measure are reported in Table 2). These three measures of average annual use during ages 22–26, which were moderately correlated with one another (Supplemental Table 1), were converted to Z-scores and averaged to form a substance use composite measure (SC) that was the main outcome measure of interest.

Several covariates were used in predictive analyses to adjust for effects of other well-known risk factors for problematic substance use, including participants' sex (0 = male, 1 = female), family history of AUD (given the enrichment of this sample with individuals who had this risk factor; 0 = no family history, 1 = AUD history for one or both parents), and participants' level of substance use prior to the time of the scan (described in detail below). As a subset of individuals were diagnosed with Attention-Deficit/Hyperactivity Disorder (ADHD; Table 2), and as individuals taking medications for ADHD were asked to cease taking their medication >48 hours prior to scanning, we also included ADHD diagnosis (0 = negative, 1 = positive) as a covariate to account for possible confounds related to the disorder or to medication withdrawal[a].

[a] ADHD diagnosis was assessed with both the Diagnostic Interview Schedule (DIS[40]) and screening questions about previous ADHD diagnosis and medication use. We used diagnostic information from the DIS for all participants except for three who did not complete this measure. We therefore used information from the screening questions to assess diagnostic status for these three participants, all of whom reported no previous ADHD diagnosis or medication use. We also note that, given the small number of participants with ADHD in the longitudinal sample (n=7), it was not feasible to account for diagnosis and medication use with separate covariates.

Prior substance use covariates were cumulative sums of the same three common substance use measures (drink volume, marijuana frequency, and cigarette frequency) from annual assessments up to and including individuals' assessment at age 17. Similar to our outcome measure, we converted these covariates to Z-scores and averaged them to form a prior substance use composite measure (preSC), which was used as a single covariate in regression models. However, we also conducted a sensitivity analysis (Supplemental Materials) in which raw scores of individual prior substance use covariates were used in place of preSC.

Inferential Analyses

We conducted all inferential analyses using JASP[41], a software package allowing users to implement frequentist and Bayesian statistical tests. We conducted analyses from both statistical frameworks in order to evaluate whether our results were sensitive to the chosen framework and to leverage Bayesian model comparison methods to obtain continuous estimates of the probability that our two variables of interest, drift rate (*v.avg*) and error-related activation (PC1), provided unique predictive information.

First, we used Pearson correlation (*r*) tests to assess whether our measure of EEA from the behavioral task (*v.avg*) displayed a positive relationship with error-related activation (PC1). These inferences were evaluated with both frequentist *p*-values, which test whether the null hypothesis (r=0) can be rejected, and Bayes factors (BF), which are continuous measures of evidence that the data provide for an alternative model/hypothesis (H_1) relative to the null model/hypothesis (H_0). The BF_{10} is intuitively interpreted as an odds ratio; a BF_{10} of 6.00 in favor of H_1 indicates that the data are 6 times more likely under H_1 than H_0, while a BF_{10} of 0.33 would indicate that the data are instead BF_{01}=3 (=1/0.33) times more likely under H_0 than H_1. In

Bayesian correlation tests, H_1 and H_0 correspond to the hypotheses that $r \neq 0$ and $r=0$, respectively[b].

Second, three separate frequentist regression analyses were conducted in which *v.avg*, PC1, and PC2, respectively, were entered along with covariates as prospective predictors of the SC measure. These analyses tested whether the null hypothesis (i.e., our predictor variables of interest are not prospectively related to SC when accounting for other previously established risk factors) could be rejected in each case. As we expected *v.avg* and PC1 to index similar individual difference dimensions, we also conducted a fourth regression analysis in which these two predictors of interest were entered simultaneously to test whether the null hypothesis could be rejected for each predictor even after accounting for effects of the other. We used false discovery rate (FDR: $q<.05$), where each separate regression was considered its own family of tests, to assess whether *p*-values from this analysis were robust to correction for multiple comparisons.

Finally, we conducted Bayesian linear regression analyses[42]. To study the relationships between the predictors of interest (*v.avg*, PC1, PC2) and the outcome SC after accounting for effects of covariates, we first added all nuisance covariates (e.g., preSC) to a "null" model. We then estimated alternative models of interest, which included these nuisance covariates as well as all possible combinations of the predictors of interest[c]. Models were then compared using BF_{10}, which quantifies the evidence in favor of each alternative model relative to the "null" model, and BF_M, which quantifies evidence for each model compared to all other models. To summarize the importance of *v.avg*, PC1 and PC2 across all models, we also performed model averaging, which provides us with evidence for inclusion, relative to non-inclusion of each variable (BF_{inc})[43,44]. Importantly, models that are averaged in this way provide evidence that is corrected for multiple

[b] All correlation tests used JASP's default *r* prior: a uniform distribution spanning the values between -1 and 1.
[c] All Bayesian regression analyses used a JZS prior, which is the default prior in JASP, as well as the default prior scale (r scale = 0.354).

testing[45,46]. These Bayesian analyses allowed us to directly test whether *v.avg* and PC1 contain unique versus redundant predictive information by quantifying evidence for a model that contains both variables relative to simpler models that contain only one of each.

Results

Summary of Error-related Activation

Results from the PCA of error-related activation in our 8 ROIs are displayed in Table 3. Five components were necessary to explain more than 90% of the variance, although the first component explained the majority (51.22%). As expected, the first component was highly correlated with error-related activation in all ROIs, and salience network structures displayed particularly strong loadings on this component, including ACC (.81), right IFG/insula (.78), and left IFG/insula (.81). Notably, striatal ROIs displayed the lowest loadings on the first component (.45 and .55), and these ROIs were, instead, selectively related to the second component (PC2). This pattern may reflect the fact that, although bilateral striatum was identified in our term-based meta-analysis as being related to the term "error," these structures are not typically associated with error monitoring or the salience network. Their identification in the meta-analysis may have been an artifact of the inclusion of the word "error" in other constructs associated with striatum (e.g., "reward prediction error"[47]). As error-related activations in ROIs previously associated with error monitoring and the salience network were strongly related to PC1, we concluded that this component would operate as an effective general summary measure of error-related activation. However, as the striatum-specific component (PC2) may be of interest as well, we also assessed this component's associations with EEA and substance use in subsequent analyses.

Neural Correlates of EEA

Consistent with findings from our previous study[29], there was evidence for a positive correlation between PC1 and *v.avg*, both in the full sample (N=143), r=.32, p<.001, BF_{10}=204.43, and when the longitudinal subsample (n=106) was considered separately, r=.25, p=.011, BF_{10}=2.87 (Figure 2b). In contrast, there was mostly evidence *against* the presence of a correlational relationship between PC2 and *v.avg*, both in the full sample, r=-.15, p=.084, BF_{10}=0.46, and longitudinal subsample, r=-.15, p=.137, BF_{10}=0.36. Hence, error-related activation from the salience network component (PC1) displayed consistent evidence of a positive relationship with EEA, as expected, but activation specific to the striatum (PC2) did not.

Frequentist Regression Analyses

In frequentist regression analyses considering each predictor of interest along with covariates (Table 4; scatterplots in Figure 2c), both *v.avg*, β=-0.21, p=.010, and PC1, β=-0.25, p=.002, were found to have statistically significant negative associations with the SC from ages 22–26, but PC2 was not, β=0.10, p=.226. In the regression that included both primary predictors of interest simultaneously, *v.avg*, β=-0.17, p=.040, and PC1, β=-0.22, p=.009, were again found to have significant relationships with the outcome, but the relationship involving *v.avg* was not robust to our correction for multiple comparisons. Although this result suggests the possibility that *v.avg* provides information that is redundant with that provided by PC1, Bayesian analyses, reported below, are needed to precisely quantify evidence for this possibility. Male sex and higher prior levels of substance use also appeared to be predictors of the SC across regressions. Together, these analyses suggest that lower levels of both individuals' drift rate (*v.avg*) and degree of error-related activation in salience network regions during the task (PC1) are prospective predictors of substance use in emerging adulthood.

Bayesian Model Comparison

Results from Bayesian regression analyses predicting the SC (Table 5) indicated that there was moderate to strong evidence for models that included *v.avg*, PC1, and both predictors simultaneously; BF_{10} indicated the observed data were 5.64, 18.21, and 34.22 times more likely under each of these models, respectively, than under the "null" (nuisance covariate only) model. In contrast, the data were less likely under the model that included PC2 only than under the "null" model, BF_{10}=0.52, and the addition of PC2 to models that included the other predictors of interest always made these models less likely, suggesting that PC2 is not predictive of the SC. BF_{10} values also indicated that the data were roughly 6.07 (34.22/5.64) times more likely under the model that simultaneously included *v.avg* and PC1 than under the model that included *v.avg* only, and 1.88 (34.22/18.21) times more likely under the two-predictor model than under the model that included PC1 only. Furthermore, BF_M values, which quantify evidence for each model compared to all other models, indicated that the data provided moderate support for the model with both predictors of interest (BF_M=4.97), comparatively modest support for the PC1 only model (BF_M=1.98), and evidence against the *v.avg* only model (BF_M=0.51). In other words, BF_{10} and BF_M indicate that, although all models involving *v.avg* and PC1 are well-supported, there is some evidence that simultaneous inclusion of both predictors leads to a better description of the data than when only one is included.

Inclusion Bayes factors (BF_{inc}) obtained via model averaging indicated positive evidence for inclusion of *v.avg*, BF_{inc}=1.93, and PC1, BF_{inc}=7.96, although evidence for the former was weaker. Finally, consideration of models' explanatory power (r^2) indicated that the model containing both *v.avg* and PC1 explained a substantially greater proportion of the variance than the "null" (covariate only) model (roughly 8% more). In sum, Bayesian analyses provide evidence that both *v.avg* and PC1 are meaningful predictors of substance use in emerging

adulthood and that each may provide unique predictive information, even when included in the same model.

Discussion

This study aimed to test whether lower efficiency of evidence accumulation (EEA), as indexed by the DDM's "drift rate" parameter[22,35], is a computationally tractable neurocognitive risk factor for frequent substance use in emerging adulthood. In a longitudinal sample, we found evidence that both lower levels of EEA and reductions in EEA's neural correlates — error-related activation in brain regions linked to salience and performance monitoring — were prospectively related to greater use of the major substances of abuse (alcohol, marijuana, cigarettes) during ages 22–26.

Our finding that EEA facilitates meaningful predictions about substance use in an age range critical for SUD development has at least two major implications. First, although other cognitive constructs have been posited as risk factors for substance use problems (e.g., inhibitory control), these constructs have recently been criticized for lacking coherence as individual difference dimensions[17,18] and for lacking links to specific computational and neural mechanisms that can explain (rather than simply describe) cognitive performance[19]. In contrast, EEA is a dimension derived from well-validated mathematical models that explain cognitive performance using formally specified and biologically plausible mechanisms[20,21], and EEA shows clear trait-like qualities when measured across a variety of tasks with different cognitive demands[23,27]. Crucially, the latter implies that the relationships identified in the current study are likely not limited to the go/no-go or other "inhibition" tasks. If low EEA proves to be a key mechanism that underlies relationships between poorer performance on a variety of neurocognitive measures and later substance use problems, researchers could leverage these well-developed computational

models and knowledge of their links to neural processes (e.g., salience network activity) to identify circuits related to addiction risk and novel pharmacological targets.

Second, our findings indicate that EEA and its neural-level correlates may each provide unique information for substance use prediction, suggesting that inclusion of both measures in cross-validated models may ultimately enhance prediction of individual-level substance use outcomes in an applied context. Our Bayesian model comparison analyses provided moderate evidence that there is added value in including neural-level correlates of EEA in prediction models, even in addition to estimates of EEA itself. Hence, future work that seeks to utilize EEA or other computationally derived risk factors to make real-world predictions about individuals' substance use problems should consider identifying neural correlates of these risk factors that can be feasibly measured in applied settings (e.g., electrophysiological measures of error-monitoring). Additionally, as recent work suggests that self-report measures have greater predictive power than task-based measures[18], identification of self-report measures that index similar mechanistic dimensions to EEA may aid prediction. Future work establishing the place of EEA in a larger nomological network of task and survey measures is therefore needed.

The neural processes involved in evidence accumulation on choice task trials are understood at the computational level as well as at the neurophysiological level[20,21]. However, investigations of systems-level correlates of EEA, as well as individual differences in EEA, are only getting started. Although EEA is likely to display multiple circuit- and systems-level neural correlates in different imaging modalities, the current study focused on error-related brain activation patterns because these were identified as the most robust neural correlates of EEA in our previous fMRI study of the go/no-go task[29]. Our finding that a summary measure of error-related activation was associated with EEA, and similarly predicted substance use outcomes, is

significant in the context of accounts linking EEA to catecholamine systems thought to regulate arousal and optimize task performance in response to feedback[48]. Brain regions involved in performance monitoring are thought to provide input to these systems[48], and connectivity of the salience network, comprised of regions that were major contributors to our summary error-related activation measure, has been specifically linked to norepinephrine action[49]. Therefore, individual differences in EEA may, in part, reflect individual differences in the integrity of catecholamine systems and associated neural networks that optimize task performance in response to external feedback or environmental demands.

This study has several limitations. First, our sample was not large enough to use cross-validation methods to assess out-of-sample accuracy of our predictive models, which is necessary to provide accurate estimates of a model's ability to predict new data in the real world. Larger samples, such as that of the Adolescent Brain Cognitive Development (ABCD) study[50], could be utilized to assess whether measures of EEA, and its neuroimaging correlates, can predict substance use in unseen data. However, ABCD is still in the early years of data collection, and substantial rates of substance initiation will not be seen for many years. A second, related, limitation is that we were unable to quantify whether our model-based EEA measure displayed greater explanatory power than standard performance-based measures from the go/no-go (e.g., mean RT, false alarm rate); the collinearity between EEA and these measures would make their simultaneous inclusion in regression models problematic at this sample size. As we note in our previous study[29], future work in larger data sets is necessary to provide precise estimates of these measures' relative predictive power. Third, although we attempted to account for possible confounds related to ADHD diagnosis and medication use in our regression analyses, the small number of individuals with the diagnosis (n=7) likely prevented us from

disentangling unique contributions of these factors from those of EEA. Fourth, we did not assess whether EEA shows a selective association with individual substances. We opted to predict a composite measure of common substance use because our sample was not large enough to identify predictors of rarer substances (e.g., opioids), or to identify distinctive predictors of the use of commonly used individual substances, measures of which were moderately correlated (Supplemental Materials). Finally, although this study indicates that EEA and its neural correlates prospectively relate to substance use, the behavioral mediators by which low EEA confers risk are not currently known.

In sum, the current study provides evidence that lower levels of EEA, a biobehavioral dimension that is derived from well-established computational models of brain function and has clear neural correlates, shows promise as a mechanistic risk factor for frequent substance use in emerging adulthood, a critical developmental period in the emergence of SUDs. These findings could inform predictive models of the emergence of substance use problems and take a crucial initial step in bringing the benefits of computational psychiatry to the developmental neuroscience of addiction.

Figures

Figure 1. Simplified schematic of the diffusion decision model (DDM) in cases with relatively high (red arrow) and relatively low (blue arrow) efficiency of evidence accumulation (EEA). The DDM assumes that responses on two-choice response time (RT) tasks and go/no-go tasks are the result of a decision variable that drifts over time, on the basis of noisy evidence gathered from the stimulus, until it reaches one of two boundaries which each represent a possible choice (e.g., the correct vs. incorrect response for a given stimulus). When decision processes on individual trials, which are represented by the light red and light blue traces, terminate at one of the boundaries, the corresponding response occurs. The boundaries are set at 0 and parameter *a*, and the decision variable begins at a starting value, set at parameter *z*. A non-decision time (*Ter*) parameter accounts for time taken up by processes peripheral to the decision (e.g., early sensory process, motor processes). The drift rate parameter (*v*) determines the average rate at which the decision variable drifts towards the boundary for the correct response, and can be used as a measure of EEA in individual differences analyses. Relative to the case with high *v*/EEA (red arrow), the case with low *v*/EEA (blue arrow) exhibits more variable RTs (a greater proportion of long RTs in the skewed right tail) and more incorrect responses. The go/no-go version of the DDM assumes the same core processes as the two-choice version, but accounts for non-responses (omissions on "go" trials and inhibitions on "no go" trials) with an implicit boundary.

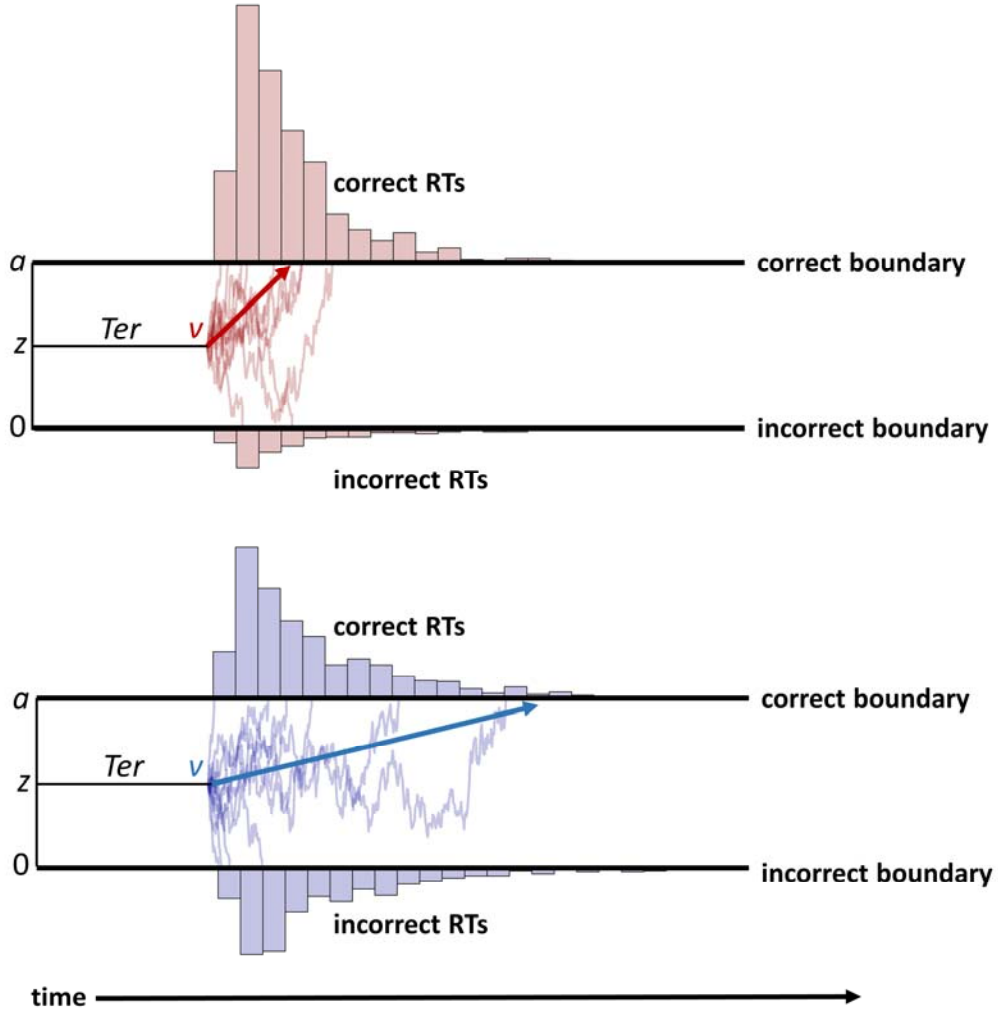
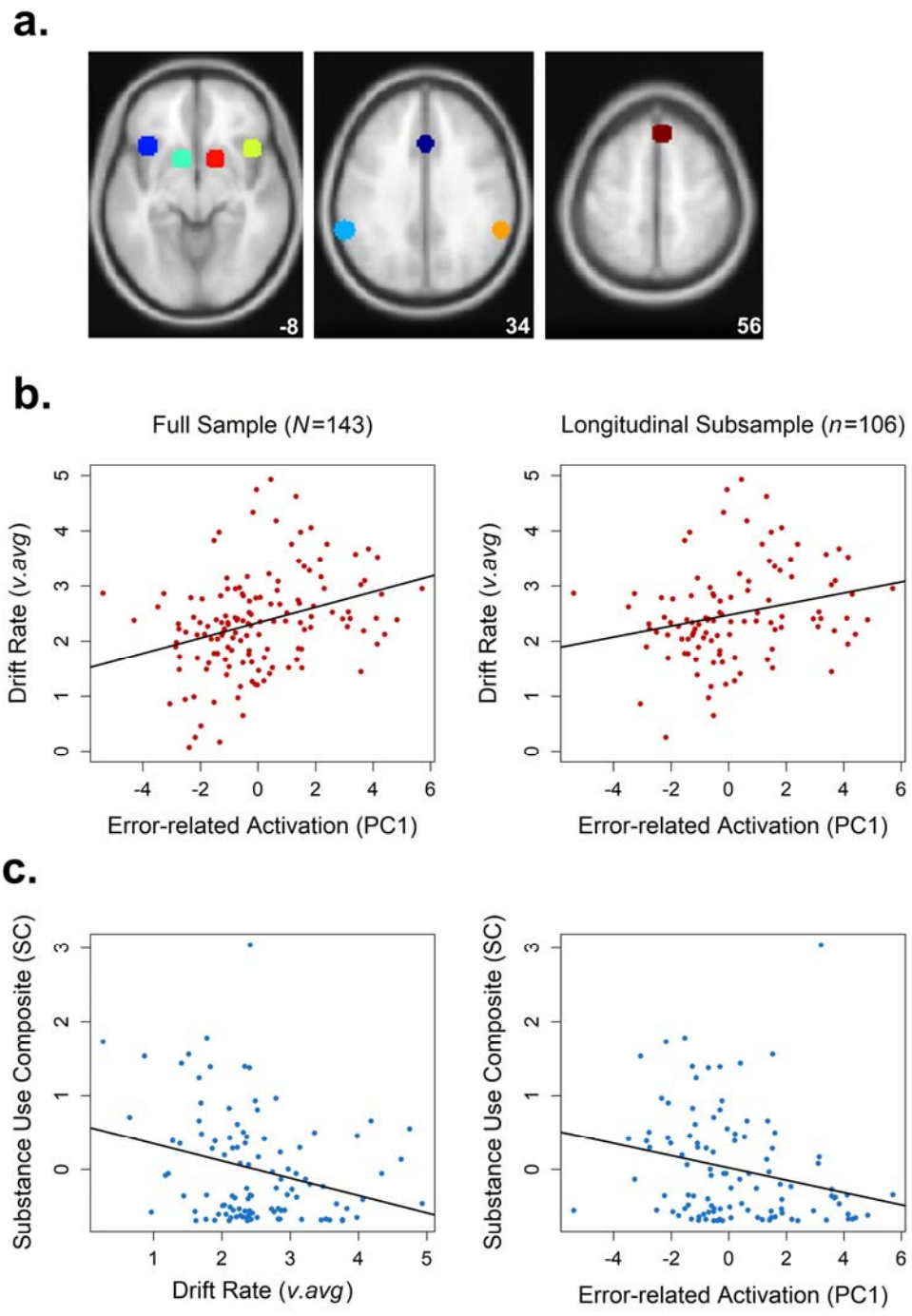


Figure 2. (**a**) Spheres (8mm radius) centered about the coordinates of our 8 regions of interest (ROIs; white numbers in lower right indicate z-coordinates). (**b**) Scatterplots of the association between our summary measure of error-related activation in these ROIs (PC1) and individuals' average drift rates (*v.avg*) from the go/no-go task for both the full sample (*N*=143) and the subsample of individuals with substance use outcome data (*n*=106) who were included in later prediction analyses. (**c**) Scatterplots of associations in which average drift rate (*v.avg*; left) and our summary measure of error-related activation (PC1; right) predict individuals' values of the age 22–26 substance use composite (SC). Simple regression lines are displayed in black.



Tables

Table 1. Abbreviations used in this study.

Abbreviations	**Full form**
ABCD	Adolescent Brain Cognitive Development study
ACC	Anterior cingulate cortex
ADHD	Attention-Deficit/Hyperactivity Disorder
AUD	Alcohol use disorder
BF	Bayes factor
DDM	Diffusion decision model
EEA	Efficiency of evidence accumulation
fMRI	functional magnetic resonance imaging
IFG	Inferior frontal gyrus
MLS	Michigan Longitudinal Study
PC1	First principal component (salience network)
PC2	Second principal component (striatum)
PCA	Principal component analysis
preSC	Previous substance use composite measure (covariate)
ROI	Region of interest
RT	Response time
SC	Substance use composite measure (outcome)
SUD	Substance use disorder
v.avg	Average drift rate

Table 2. Demographic information and summary statistics (means with standard deviations in parentheses) of all DDM parameters and variables included in prediction analyses. Demographics and statistics are reported separately for both the full sample included in the PCA of neural activation (*N*=143) and the subsample with available substance use outcome data (*n*=106), which was the focus of predictive analyses. "Annual" substance use measures were averaged over all available assessments from ages 22–26, and the "# of Measurements" rows report the mean number of measurement time points available per person for each substance use variable. AUD FHx = family history of alcohol use disorder (either parent); ADHD Dx = Attention-Deficit/Hyperactivity Disorder diagnosis; Cu. = cumulative sum of each substance use measure up to and including participants' assessment at age 17

Demographics/Measures	**Full Sample (*N*=143)**	**Longitudinal Subsample (*n*=106)**
Sex (Male/Female)	87/56	63/43
Age at scan	19.66 (1.22)	19.89 (1.20)
Race/Ethnicity		
Caucasian	128	102
Hispanic/Latino	5	2
African American	6	2
Other/bi-racial	4	0
AUD FHx (Positive/Negative/Unknown)	108/34/1	78/28/0
ADHD Dx	15	7
Drift rate for "go" stimuli (*v.go*)	2.77 (1.03)	2.95 (1.03)
Drift rate for "no-go" stimuli (*v.nogo*)*	1.90 (0.88)	2.04 (0.80)
Average drift rate for all stimuli (*v.avg*)	2.34 (0.88)	2.50 (0.86)
Boundary separation (*a*)	1.00 (0.21)	1.00 (0.21)
Non-decision time (*Ter*)	.317 (.032)	.314 (.031)
Response bias (*z*)	0.62 (0.07)	0.62 (0.07)
Annual Drink Volume (ages 22–26)	---	429.91 (451.68)
Annual Marijuana Frequency (ages 22–26)	---	38.98 (83.70)
Annual Cigarette Frequency (ages 22–26)	---	89.14 (136.08)
# of Drink Volume Measurements	---	4.00 (1.32)
# of Marijuana Frequency Measurements	---	4.01 (1.33)
# of Cigarette Frequency Measurements	---	4.03 (1.33)
Cu. Drink Volume (at age 17)	312.86 (781.19)	381.70 (764.87)
Cu. Marijuana Frequency (at age 17)	60.99 (178.93)	48.38 (130.87)
Cu. Cigarette Frequency (at age 17)	145.55 (356.51)	147.26 (351.81)

*=Multiplied by -1 for comparability to *v.go*

Table 3. Variance explained by, and loadings of each region of interest (ROI) on, the five principal components (PCs) that together explain over 90% of between-subject variation in error-related ROI activations. MNI coordinates of ROIs are displayed in parentheses. L. = left; R. = right; IFG = inferior frontal gyrus; SMA = supplementary motor area

Variance Explained	**PC1**	**PC2**	**PC3**	**PC4**	**PC5**
% explained by component	51.22	18.79	9.34	7.66	4.86
cumulative % explained	51.22	70.01	79.35	87.02	91.87
ROI (x, y, z) Loadings	**PC1**	**PC2**	**PC3**	**PC4**	**PC5**
Anterior Cingulate (0,22,38)	0.81	-0.05	0.05	-0.24	-0.52
L. Insula/IFG (-38,20,-6)	0.81	-0.21	-0.43	0.08	0.15
L. Parietal (-62,-44,34)	0.77	-0.25	0.35	0.29	-0.03
L. Striatum (-12,10,-10)	0.45	0.83	-0.01	0.08	-0.04
R. Insula/IFG (42,18,-6)	0.78	-0.26	-0.49	0.06	0.01
R. Parietal (58,-44,30)	0.75	-0.26	0.40	0.24	0.13
R. Striatum (14,10,-10)	0.55	0.75	-0.02	0.14	0.07
R. pre-SMA (4,30,54)	0.71	0.03	0.19	-0.61	0.27

Table 4. Results from frequentist regression analyses predicting values of the age 22–26 substance use composite (SC) with models that included 1) *v.avg*, 2) PC1, 3) PC2 and 4) both EEA-related predictors of interest (*v.avg* and PC1) simultaneously, along with covariates. **Bolded** *p*-values survive false discovery rate correction for multiple comparisons within families defined by the individual regression models. Overall variance explained by each model (r^2) is displayed in parentheses. AUD FHx = family history of alcohol use disorder (either parent); ADHD Dx = Attention-Deficit/Hyperactivity Disorder diagnosis; preSC = prior substance use composite (cumulative use through age 17)

Model (r^2)		Unstandardized	Standard Error	Standardized	*T*	*p*
v.avg	(Intercept)	0.513	0.201			
(.378)	Sex	-0.281	0.117	-0.191	-2.407	**0.018**
	AUD FHx	0.041	0.132	0.025	0.310	0.757
	ADHD Dx	0.320	0.234	0.110	1.368	0.174
	preSC	0.410	0.065	0.501	6.312	**< .001**
	v.avg	-0.180	0.069	-0.214	-2.625	**0.010**
PC1	(Intercept)	0.060	0.126			
(.393)	Sex	-0.244	0.116	-0.166	-2.101	0.038
	AUD FHx	0.054	0.131	0.033	0.413	0.680
	ADHD Dx	0.314	0.231	0.108	1.358	0.177
	preSC	0.439	0.064	0.538	6.858	**< .001**
	PC1	-0.086	0.028	-0.251	-3.106	**0.002**
PC2	(Intercept)	0.149	0.135			
(.345)	Sex	-0.323	0.123	-0.219	-2.631	**0.010**
	AUD FHx	-0.052	0.137	-0.032	-0.380	0.704
	ADHD Dx	0.371	0.240	0.128	1.548	0.125
	preSC	0.427	0.066	0.522	6.427	**< .001**
	PC2	0.057	0.047	0.103	1.219	0.226
v.avg	(Intercept)	0.388	0.201			
and	Sex	-0.243	0.114	-0.165	-2.126	0.036
PC1	AUD FHx	0.091	0.130	0.055	0.698	0.487
(.419)	ADHD Dx	0.259	0.229	0.089	1.134	0.259
	preSC	0.426	0.063	0.521	6.721	**< .001**
	v.avg	-0.142	0.068	-0.169	-2.086	0.040
	PC1	-0.074	0.028	-0.215	-2.648	**0.009**

Table 5. Results of the Bayesian regression analyses in which all possible models involving the predictors of interest, drift rate (*v.avg*), general error-related activation (PC1), and activation specific to the striatum (PC2), were compared to a "null" model that included only the covariates of sex, family history of alcohol use disorder (AUD FHx), Attention-Deficit/Hyperactivity Disorder diagnosis (ADHD Dx), and the prior substance use composite (preSC). Note that all models contain these covariates in addition to any predictors of interest. In the "Model Comparison" section, P(M) is prior probability of the model, P(M|data) is the posterior probability of the model after seeing the data, BF_{10} is the Bayes factor comparing the model to the "null" model, and BF_M is a Bayes factor comparing the model to all other models from the analysis. The "Posterior Summaries" section reports the model-averaged mean, standard deviation (SD) and 95% credible intervals of posterior samples for coefficients of each predictor of interest, as well as inclusion probabilities obtained from model averaging; P(inc) is the prior probability of including each predictor, P(inc|data) is the posterior probability of including each predictor, and BF_{inc} is a Bayes factor for the change from prior to posterior inclusion odds for the predictor after seeing the data.

Model Comparison

Models	P(M)	P(M|data)	BF_M	BF_{10}	r^2
"Null" (Sex, AUD FHx, ADHD Dx, preSC)	0.125	0.012	0.086	1.000	0.335
v.avg + PC1	0.125	0.415	4.968	34.222	0.419
PC1	0.125	0.221	1.984	18.208	0.393
v.avg + PC1 + PC2	0.125	0.150	1.238	12.389	0.422
PC1 + PC2	0.125	0.102	0.797	8.427	0.401
v.avg	0.125	0.068	0.514	5.637	0.378
v.avg + PC2	0.125	0.025	0.177	2.039	0.382
PC2	0.125	0.006	0.045	0.522	0.345

Posterior Summaries of Coefficients

						95% Credible Interval	
Coefficient	**Mean**	**SD**	**P(inc)**	**P(inc|data)**	**BF_{inc}**	**Lower**	**Upper**
v.avg	-0.087	0.083	0.500	0.658	1.928	-0.251	0.000
PC1	-0.063	0.034	0.500	0.888	7.963	-0.117	0.000
PC2	0.010	0.028	0.500	0.284	0.396	-0.026	0.088

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Author Contributions

RAZ and MH designed the larger study and acquired data for the data set that was utilized in the current work. AW, MH and CS conceptualized the research questions and analyses. AW analyzed and the data with assistance and consultation from AL and under the supervision of MH and CS. All authors were involved in interpretation of the analyses. AW, SB, MM, and LC wrote the first draft of the paper, and JH, AL, RAZ, CS and MH provided critical revisions. All authors approved the final version of the manuscript for submission and agree to be accountable for all aspects of the work.

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Supplemental Materials for:

Evidence accumulation and associated error-related brain activity as computationally informed prospective predictors of substance use in emerging adulthood

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Go/No-Go Task

Participants completed an event-related go/no-go task[1–3] during fMRI data collection in which they were presented with a string of letters (white on black background) that indicated whether they should respond (any letter other than "X"; 75% of trials) or inhibit their response ("X"; 25% of trials). Letters were presented for 500ms (3500ms interstimulus fixation interval) during 5 imaging runs of 49 trials each (245 trials total; 60 "X" trials).

MRI Data Acquisition Parameters

A high-resolution T1-weighted anatomical image was obtained using the following parameters: three-dimensional spoiled gradient-recalled echo, TR=25ms, minimum TE, FOV=25cm, 256x256 matrix, slice thickness=1.4mm. During runs of the go/no-go task, whole brain T2*-weighted functional images were acquired using a single-shot spiral in-out sequence[4] with the following parameters: TR=2000ms, TE=30ms, flip angle=90°, FOV=200mm, 29 axial slices, 64×64 matrix, in-plane resolution=3.12mm×3.12mm, and slice thickness=4mm. All scans were conducted with the same 3.0 T GE Signa scanner.

Pre-Processing and Single-Subject fMRI Analyses

Functional images were reconstructed using an iterative algorithm[5] and entered into the following pre-processing steps: 1) motion correction with realignment using FSL 5.0.2.2 tools (FMRIB, Oxford, United Kingdom), 2) spatial normalization to standard space as defined by the Montreal Neurological Institute template using Statistical Parametric Mapping 8 (SPM8: Wellcome Institute of Cognitive Neurology, London, United Kingdom) and using normalization of the T1-weighted anatomical image for guidance, 3) resampling to 2x2x2mm voxels in SPM8, and 4) spatial smoothing with a 6mm full-width half-maximum Gaussian kernel. Functional runs

were excluded from further analysis if they exceeded 3 mm translation or 3° rotation in any direction during the run.

A general linear model was fit in SPM8 to individual subjects' fMRI time series data with three regressors convolved with the hemodynamic response function: 1) "go" responses, 2) successful inhibition (SI) trials, in which participants withheld their response to a "no-go" stimuli, and 3) failed inhibition (FI) trials, in which participants made a response following "no-go" stimuli. Motion parameters from earlier realignment and average white matter signal intensity for each volume were also included as nuisance regressors. Individual statistical maps for the primary "error monitoring" contrast of interest (FI > correct "go") were generated for later analyses.

Correlations Between Raw and Composite Substance Use Measures

We investigated simple correlations between all individual and composite substance use outcome measures of interest from ages 22–26 in order to 1) evaluate whether they were moderately correlated with each other, as would be expected given prior research, and 2) ensure that our substance use composite (SC) measure was well-representative of the use of all three substances. We also did the same with measures of prior cumulative use of all three substances from age 17 and the prior substance use composite (preSC) that was utilized as a covariate in the primary analyses. Supplemental Table 1 displays Bayesian estimates of correlation coefficients between all of these variables. Inspection of these values indicates that, as expected, measures of average use of all three substances from ages 22–26 are moderately correlated with one another, and measures of cumulative use by age 17 also show strong interrelationships. Furthermore, both the SC and preSC show strong, and roughly equal, correlations with the three substance use measures that each composite measure was derived from, suggesting that these composites

provide representative indices of the use of common substances for specific developmental periods.

Sensitivity Analyses

To assess whether our findings were robust to the inclusion of prior substance use and other covariates in our prediction models, we conducted two sensitivity analyses using the same frequentist and Bayesian methods that were utilized in the primary analyses. First, we conducted prediction analyses which used measures of cumulative use of individual substances by age 17 (alcohol, marijuana, cigarettes) as covariates, in place of the preSC, in order to evaluate whether our findings would hold when prior use of these substances was accounted for individually (Supplemental Tables 2–4). Next, we conducted prediction analyses without any of our previous covariates to evaluate whether our results were still robust even when models did not account for other relevant risk factors (Supplemental Tables 5 and 6).

Results of the first sensitivity analysis are highly similar to the results of our primary analyses reported in the manuscript; both predictors of interest, *v.avg* and PC1, show statistically significant relationships with the SC outcome in frequentist tests, and Bayesian model comparison indicates substantial evidence for the inclusion of both predictors of interest in the model. Results of our second sensitivity analysis, without any covariates, were also similar, although there was slightly less evidence for the inclusion of the neural-level measure (PC1). However, the best-fitting model was still one which contained both predictors of interest, rather than *v.avg* only. Taken together, results from these sensitivity analyses suggest that our primary results are generally robust to the inclusion, vs. exclusion, of covariates in our regression models, and to alterations in the measurement of the prior substance use covariates, specifically.

Individual Regions of Interest as Predictors of Substance Use

We opted to use a network-based approach, in which a latent component score that was informed by activation across multiple regions of interest (ROIs) linked to error monitoring provided our primary measure of error-related activation, for our main analyses due to its advantages relative to traditional univariate approaches. Nonetheless, we also appreciate that readers may be interested in whether activation estimates from individual ROIs display more selective prospective relationships with substance use behaviors. We did not attempt Bayesian model comparison analyses to investigate this possibility because we were concerned that the high degree of collinearity between many pairs of ROIs (r>.50) would render models that included these ROIs uninformative. However, to provide preliminary indications of which ROIs may display more selective relationships with substance use, we conducted eight separate frequentist regression analyses involving each individual ROI along with covariates (Supplemental Tables 7–8). These analyses indicated that only the bilateral insula/IFG ROIs demonstrated prospective relationships with substance use that survived correction for multiple comparisons, although the anterior cingulate and bilateral parietal ROIs also displayed indications of weaker prospective relationships.

Supplemental Tables

Supplemental Table 1. Correlations between measures of the use of individual substances, both averaged over ages 22–26 and cumulative use (Cu.) by age 17, as well as with the age 22–26 average substance use composite (SC) and age 17 prior substance use composite (preSC). Large-font numbers indicate the median of the Bayesian posterior distribution of the correlation coefficient, representing the most likely correlation value, while smaller-font numbers in italics indicate the 95% credible intervals of the posterior distribution, which represent the upper and lower bounds of the range in which there is a .95 probability that the correlation coefficient falls. DV = annual volume of alcoholic drinks (standard beverages); MF = annual marijuana use frequency (days of use); CF = annual cigarette use frequency (days of use)

	DV (22–26)	MF (22–26)	CF (22–26)	SC (22–26)	Cu. DV (17)	Cu. MF (17)	Cu. CF (17)
DV (22–26)	—						
	—						
	—						
MF (22–26)	0.24	—					
	0.41	—					
	0.05	—					
CF (22–26)	0.34	0.29	—				
	0.49	*0.45*	—				
	0.16	*0.10*	—				
SC (22–26)	0.73	0.70	0.75	—			
	0.80	*0.78*	*0.82*	—			
	0.62	*0.59*	*0.64*	—			
Cu. DV (17)	0.60	0.28	0.26	0.53	—		
	0.71	*0.45*	*0.43*	*0.65*	—		
	0.46	*0.10*	*0.08*	*0.37*	—		
Cu. MF (17)	0.40	0.39	0.24	0.47	0.71	—	
	0.55	*0.53*	*0.41*	*0.60*	*0.79*	—	
	0.23	*0.21*	*0.05*	*0.30*	*0.60*	—	
Cu. CF (17)	0.29	0.24	0.33	0.39	0.70	0.64	—
	0.45	*0.40*	*0.49*	*0.54*	*0.79*	*0.73*	—
	0.11	*0.05*	*0.15*	*0.22*	*0.59*	*0.50*	—
preSC (17)	0.49	0.34	0.31	0.52	0.91	0.88	0.88
	0.61	*0.49*	*0.47*	*0.64*	*0.94*	*0.92*	*0.91*
	0.32	*0.16*	*0.13*	*0.36*	*0.86*	*0.83*	*0.82*

Supplemental Table 2. Results from our first sensitivity analysis, which included measures of prior use of individual substances as covariates rather than a prior use composite, involving frequentist regressions that predicted values of the age 22–26 substance use composite (SC) with models that included 1) *v.avg* and 2) PC1, along with covariates. **Bolded** *p*-values survive false discovery rate correction for multiple comparisons within families defined by the individual regression models. Overall variance explained by each model (R^2) is displayed in parentheses. AUD FHx = family history of alcohol use disorder (either parent); ADHD Dx = Attention-Deficit/Hyperactivity Disorder diagnosis; Cu. DV = cumulative drink volume at age 17; Cu. MJ = cumulative marijuana use at age 17; Cu. CF = cumulative cigarette use at age 17

Model (r^2)		**Unstandardized**	**Standard Error**	**Standardized**	***t***	***p***
v.avg	(Intercept)	0.492	0.200			
(.397)	Sex	-0.243	0.118	-0.165	-2.055	0.043
	AUD FHx	0.073	0.134	0.045	0.546	0.586
	ADHD Dx	0.334	0.236	0.115	1.416	0.160
	Cu. DV (17)	0.273	0.093	0.376	2.935	**0.004**
	Cu. MJ (17)	0.128	0.086	0.176	1.484	0.141
	Cu. CF (17)	0.003	0.086	0.004	0.034	0.973
	v.avg	-0.188	0.069	-0.223	-2.737	**0.007**
PC1	(Intercept)	0.017	0.127			
(.416)	Sex	-0.201	0.118	-0.137	-1.71	0.090
	AUD FHx	0.088	0.132	0.054	0.670	0.505
	ADHD Dx	0.331	0.231	0.114	1.43	0.156
	Cu. DV (17)	0.300	0.092	0.413	3.268	**0.001**
	Cu. MJ (17)	0.127	0.085	0.175	1.497	0.138
	Cu. CF (17)	0.007	0.085	0.010	0.082	0.934
	PC1	-0.091	0.028	-0.266	-3.299	**0.001**

Supplemental Table 3. Results from our first sensitivity analysis, which included measures of prior use of individual substances as covariates rather than a prior use composite, involving frequentist regressions that predicted values of the age 22–26 substance use composite (SC) with models that included 1) PC2, 2) both main predictors of interest (*v.avg* and PC1) simultaneously, along with covariates. **Bolded** *p*-values survive false discovery rate correction for multiple comparisons within families defined by the individual regression models. Overall variance explained by each model (R^2) is displayed in parentheses. AUD FHx = family history of alcohol use disorder (either parent); ADHD Dx = Attention-Deficit/Hyperactivity Disorder diagnosis; Cu. DV = cumulative drink volume at age 17; Cu. MJ = cumulative marijuana use at age 17; Cu. CF = cumulative cigarette use at age 17

Model (r^2)		**Unstandardized**	**Standard Error**	**Standardized**	***t***	***p***
PC2	(Intercept)	0.121	0.135			
(.368)	Sex	-0.291	0.123	-0.198	-2.375	0.020
	AUD FHx	-0.031	0.137	-0.019	-0.224	0.823
	ADHD Dx	0.377	0.241	0.129	1.564	0.121
	Cu. DV (17)	0.295	0.096	0.407	3.077	**0.003**
	Cu. MJ (17)	0.135	0.089	0.186	1.519	0.132
	Cu. CF (17)	-0.009	0.091	-0.012	-0.098	0.922
	PC2	0.078	0.048	0.141	1.621	0.108
v.avg	(Intercept)	0.356	0.199			
and	Sex	-0.197	0.115	-0.134	-1.710	0.091
PC1	AUD FHx	0.131	0.131	0.080	1.001	0.319
(.443)	ADHD Dx	0.269	0.229	0.093	1.177	0.242
	Cu. DV (17)	0.295	0.090	0.406	3.273	**0.001**
	Cu. MJ (17)	0.135	0.083	0.186	1.629	0.107
	Cu. CF (17)	-0.011	0.083	-0.015	-0.128	0.899
	v.avg	-0.149	0.068	-0.176	-2.196	0.030
	PC1	-0.079	0.028	-0.230	-2.845	**0.005**

Supplemental Table 4. Results from our first sensitivity analysis, which included measures of prior use of individual substances as covariates rather than a prior use composite, where Bayesian regression models that involved all combinations of predictors of interest, drift rate (*v.avg*), error-related activation (PC1), and activation specific to the striatum (PC2), were compared to a "null" model that included only the covariates of sex, family history of alcohol use disorder (AUD FHx), Attention-Deficit/Hyperactivity Disorder diagnosis (ADHD Dx), and separate measures of prior alcohol (DV), marijuana (MJ) and cigarette use (CF). In the "Model Comparison" section, P(M) is prior probability of the model, P(M|data) is the posterior probability of the model after seeing the data, BF_{10} is the Bayes factor comparing the model to the "null" model, and BF_M is a Bayes factor comparing the model to all other models from the analysis. The "Posterior Summaries" section reports the model-averaged mean, standard deviation (SD) and 95% credible intervals of posterior samples for coefficients of each predictor of interest, as well as inclusion probabilities obtained from model averaging; P(inc) is the prior probability of including each predictor, P(inc|data) is the posterior probability of including each predictor, and BF_{inc} is a Bayes factor for the change from prior to posterior inclusion odds for the predictor after seeing the data.

Model Comparison

Models	P(M)	P(M|data)	BF_M	BF_{10}	r^2
"Null" (Sex, AUD FHx, ADHD Dx, DV, MJ, CF)	0.125	0.005	0.033	1.000	0.351
v.avg + PC1	0.125	0.385	4.381	81.225	0.443
PC1	0.125	0.247	2.302	52.221	0.453
v.avg + PC1 + PC2	0.125	0.153	1.266	32.308	0.416
PC1 + PC2	0.125	0.145	1.183	30.506	0.431
v.avg	0.125	0.038	0.273	7.931	0.397
v.avg + PC2	0.125	0.023	0.164	4.823	0.406
PC2	0.125	0.005	0.033	0.990	0.368

Posterior Summaries of Coefficients

						95% Credible Interval	
Coefficient	Mean	SD	P(inc)	P(inc|data)	BF_{inc}	Lower	Upper
v.avg	-0.091	0.082	0.500	0.693	2.256	-0.240	0.000
PC1	-0.069	0.032	0.500	0.930	13.311	-0.114	0.000
PC2	0.024	0.040	0.500	0.420	0.723	-0.006	0.138

Supplemental Table 5. Results from our second sensitivity analysis, which included no covariates for other substance use risk factors, involving frequentist regressions that predicted values of the age 22–26 substance use composite (SC) with models that included 1) *v.avg*, 2) PC1, 3) PC2, and 4) both main predictors of interest. **Bolded** *p*-values survive false discovery rate correction for multiple comparisons within families defined by the individual regression models. Overall variance explained by each model (R^2) is displayed in parentheses.

Model (r^2)		**Unstandardized**	**Standard Error**	**Standardized**	***t***	***p***
v.avg	(Intercept)	0.582	0.210			
(.076)	*v.avg*	-0.233	0.080	-0.276	-2.931	**0.004**
PC1	(Intercept)	0.020	0.069			
(.059)	PC1	-0.083	0.033	-0.243	-2.554	**0.012**
PC2	(Intercept)	0.002	0.071			
(.004)	PC2	0.034	0.054	0.061	0.620	0.536
v.avg	(Intercept)	0.501	0.211			
+ **PC1**	*v.avg*	-0.195	0.081	-0.230	-2.403	**0.018**
(.109)	PC1	-0.064	0.033	-0.186	-1.944	0.055

Supplemental Table 6. Results from our second sensitivity analysis, which included no covariates for other substance use risk factors, involving Bayesian regression analyses in which all possible models involving predictors of interest, drift rate (*v.avg*), error-related activation (PC1), and activation specific to the striatum (PC2), were compared to a "null" model that included only the regression intercept parameter. In the "Model Comparison" section, P(M) is prior probability of the model, P(M|data) is the posterior probability of the model after seeing the data, BF_{10} is the Bayes factor comparing the model to the "null" model, and BF_M is a Bayes factor comparing the model to all other models from the analysis. The "Posterior Summaries" section reports the model-averaged mean, standard deviation (SD) and 95% credible intervals of posterior samples for coefficients of each predictor of interest, as well as inclusion probabilities obtained from model averaging; P(inc) is the prior probability of including each predictor, P(inc|data) is the posterior probability of including each predictor, and BF_{inc} is a Bayes factor for the change from prior to posterior inclusion odds for the predictor after seeing the data.

Model Comparison

Models	P(M)	P(M|data)	BF_M	BF_{10}	r^2
"Null" (intercept only)	0.125	0.031	0.221	1.000	0.000
v.avg + PC1	0.125	0.365	4.020	11.903	0.109
v.avg	0.125	0.267	2.552	8.717	0.076
v.avg + PC1 + PC2	0.125	0.114	0.898	3.712	0.110
PC1	0.125	0.110	0.869	3.605	0.059
v.avg + PC2	0.125	0.071	0.532	2.305	0.077
PC1 + PC2	0.125	0.035	0.254	1.144	0.062
PC2	0.125	0.007	0.053	0.244	0.004

Posterior Summaries of Coefficients

						95% Credible Interval	
Coefficient	Mean	SD	P(inc)	P(inc|data)	BF_{inc}	Lower	Upper
v.avg	-0.154	0.102	0.500	0.816	4.444	-0.324	0.000
PC1	-0.038	0.039	0.500	0.624	1.660	-0.116	0.000
PC2	0.003	0.024	0.500	0.227	0.294	-0.041	0.079

Supplemental Table 7. Results from frequentist regression analyses predicting values of the age 22–26 substance use composite (SC) with models that included activation estimates from 1) anterior cingulate cortex (ACC), 2) left insula / inferior frontal gyrus (LI/IFG), 3) right insula / inferior frontal gyrus (RI/IFG), and 4) the pre-supplementary motor area (PSMA), along with covariates. **Bolded** *p*-values survive false discovery rate correction for multiple comparisons within families defined by the individual regression models. Overall variance explained by each model (r^2) is displayed in parentheses. AUD FHx = family history of alcohol use disorder (either parent); ADHD Dx = Attention-Deficit/Hyperactivity Disorder diagnosis; preSC = prior substance use composite (cumulative use through age 17)

Model (r^2)		Unstandardized	Standard Error	Standardized	*T*	*p*
ACC	(Intercept)	0.215	0.135			
(.374)	Sex	-0.241	0.119	-0.164	-2.030	0.045
	AUD FHx	0.022	0.132	0.013	0.165	0.869
	ADHD Dx	0.371	0.233	0.128	1.593	0.114
	preSC	0.436	0.065	0.534	6.709	**< .001**
	ACC	-0.054	0.022	-0.203	-2.505	0.014
LI/IFG	(Intercept)	0.287	0.131			
(.422)	Sex	-0.324	0.113	-0.220	-2.872	**0.005**
	AUD FHx	0.063	0.127	0.038	0.493	0.623
	ADHD Dx	0.217	0.229	0.074	0.946	0.346
	preSC	0.437	0.062	0.535	6.999	**< .001**
	LI/IFG	-0.089	0.023	-0.308	-3.876	**< .001**
RI/IFG	(Intercept)	0.330	0.142			
(.401)	Sex	-0.318	0.115	-0.216	-2.767	**0.007**
	AUD FHx	0.02	0.128	0.012	0.153	0.878
	ADHD Dx	0.253	0.232	0.087	1.090	0.278
	preSC	0.431	0.063	0.527	6.790	**< .001**
	RI/IFG	-0.078	0.023	-0.265	-3.332	**0.001**
PSMA	(Intercept)	0.127	0.133			
(.340)	Sex	-0.288	0.120	-0.196	-2.391	**0.019**
	AUD FHx	0.006	0.138	0.004	0.047	0.963
	ADHD Dx	0.399	0.239	0.137	1.669	0.098
	preSC	0.434	0.068	0.532	6.412	**< .001**
	PSMA	-0.020	0.024	-0.071	-0.834	0.406

Supplemental Table 8. Results from frequentist regression analyses predicting values of the age 22–26 substance use composite (SC) with models that included activation estimates from 1) left parietal lobe (LPar), 2) right parietal lobe (RPar), 3) left striatum (LStri), and 4) right striatum (RStri), along with covariates. **Bolded** *p*-values survive false discovery rate correction for multiple comparisons within families defined by the individual regression models. Overall variance explained by each model (r^2) is displayed in parentheses. AUD FHx = family history of alcohol use disorder (either parent); ADHD Dx. = Attention-Deficit/Hyperactivity Disorder diagnosis; preSC = prior substance use composite (cumulative use through age 17)

Model (r^2)		Unstandardized	Standard Error	Standardized	*T*	*p*
LPar	(Intercept)	0.213	0.136			
(.370)	Sex	-0.238	0.120	-0.162	-1.986	0.050
	AUD FHx	-0.006	0.131	-0.004	-0.046	0.964
	ADHD Dx	0.349	0.235	0.120	1.486	0.140
	preSC	0.433	0.065	0.530	6.644	**< .001**
	LPar	-0.076	0.032	-0.192	-2.357	0.020
RPar	(Intercept)	0.221	0.138			
(.368)	Sex	-0.256	0.119	-0.174	-2.156	0.033
	AUD FHx	-0.016	0.131	-0.010	-0.119	0.906
	ADHD Dx	0.365	0.234	0.125	1.556	0.123
	preSC	0.428	0.065	0.523	6.554	**< .001**
	RPar	-0.075	0.033	-0.183	-2.276	0.025
LStri	(Intercept)	0.061	0.147			
(.338)	Sex	-0.268	0.125	-0.182	-2.139	0.035
	AUD FHx	0.006	0.139	0.003	0.041	0.967
	ADHD Dx	0.413	0.240	0.142	1.724	0.088
	preSC	0.426	0.067	0.521	6.377	**< .001**
	LStri	-0.035	0.054	-0.057	-0.655	0.514
RStri	(Intercept)	0.069	0.142			
(.338)	Sex	-0.275	0.123	-0.187	-2.24	0.027
	AUD FHx	<.001	0.138	<.001	0.004	0.997
	ADHD Dx	0.405	0.239	0.139	1.694	0.093
	preSC	0.422	0.067	0.516	6.314	**< .001**
	RStri	-0.035	0.054	-0.055	-0.648	0.518

Supplemental References

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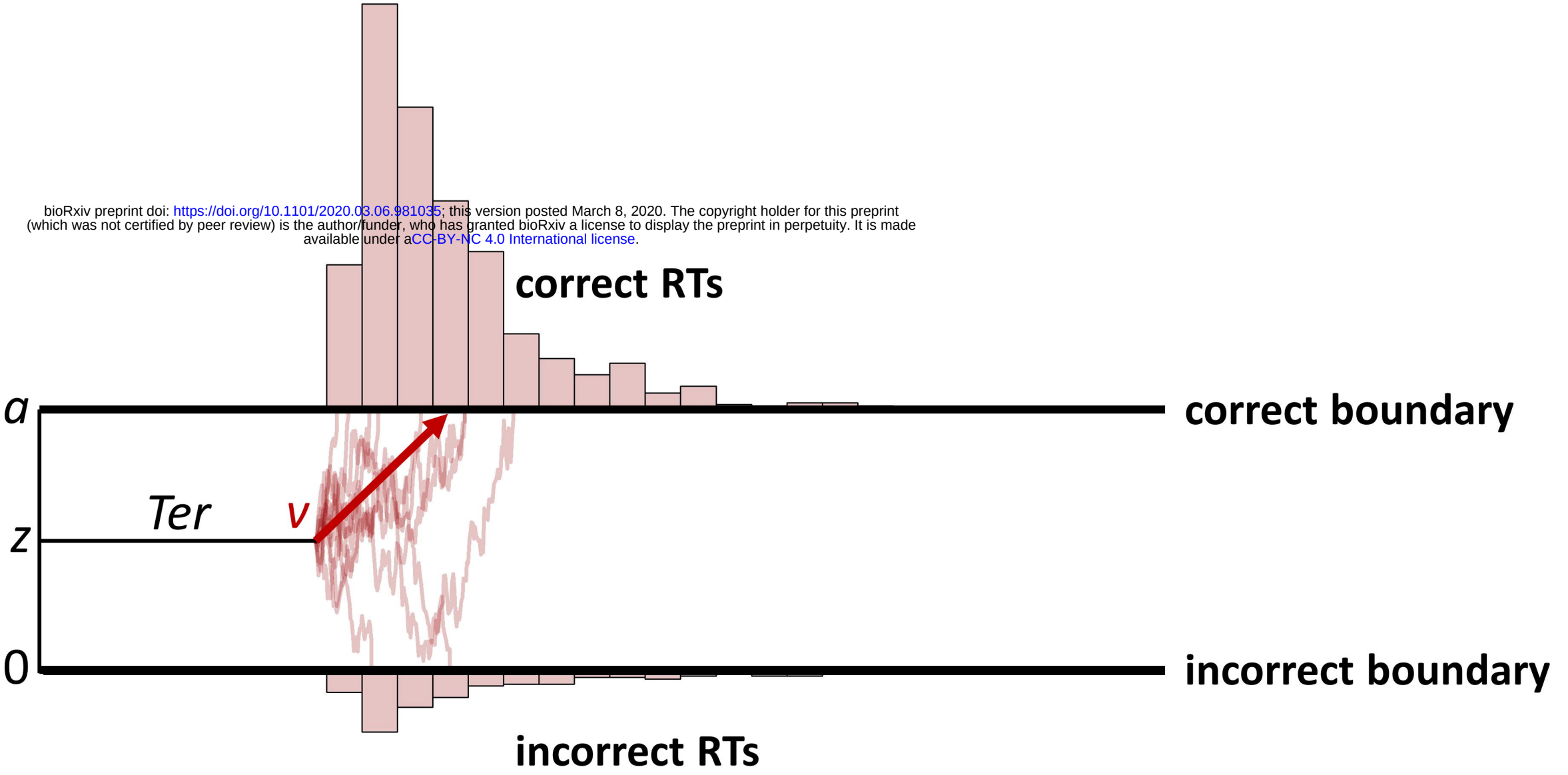

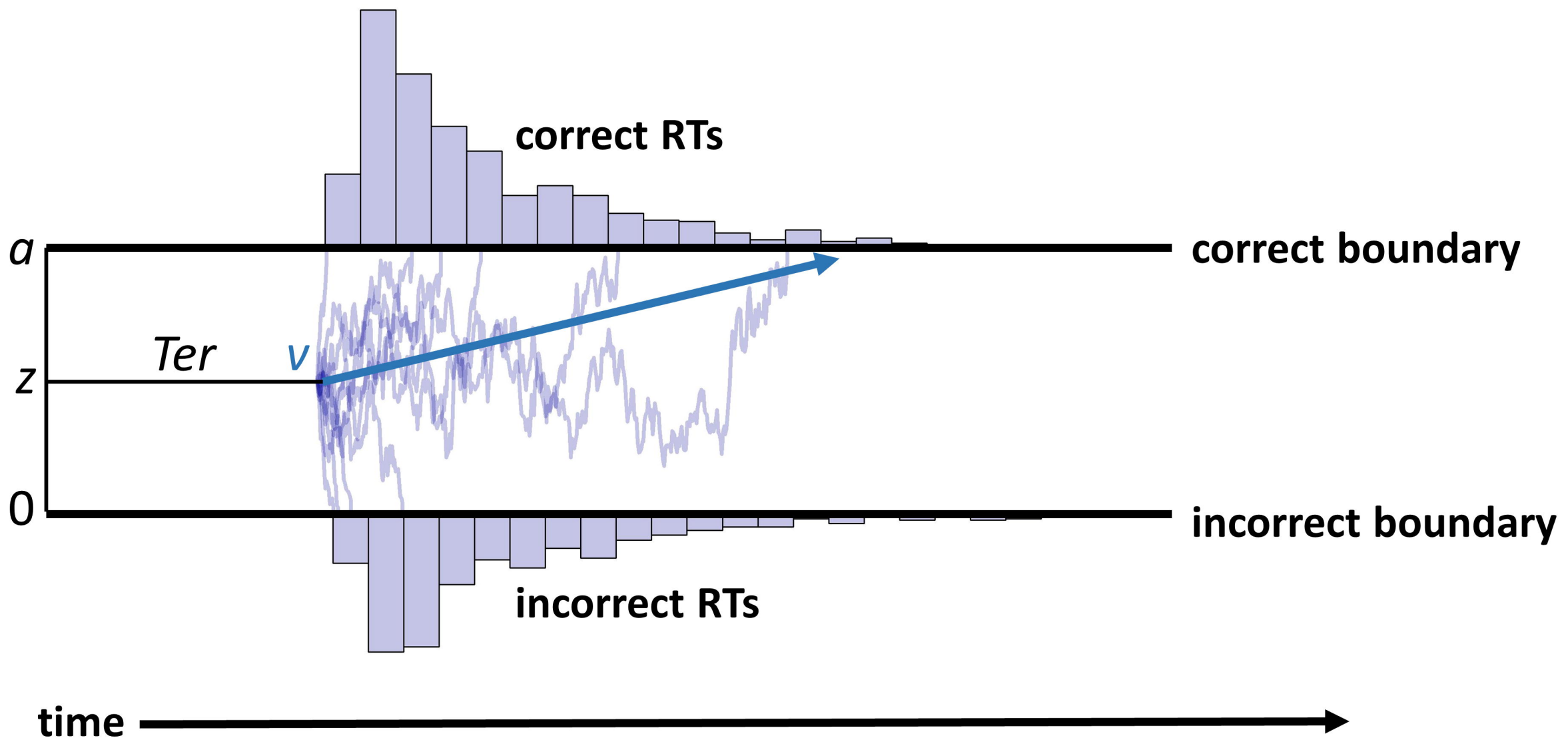

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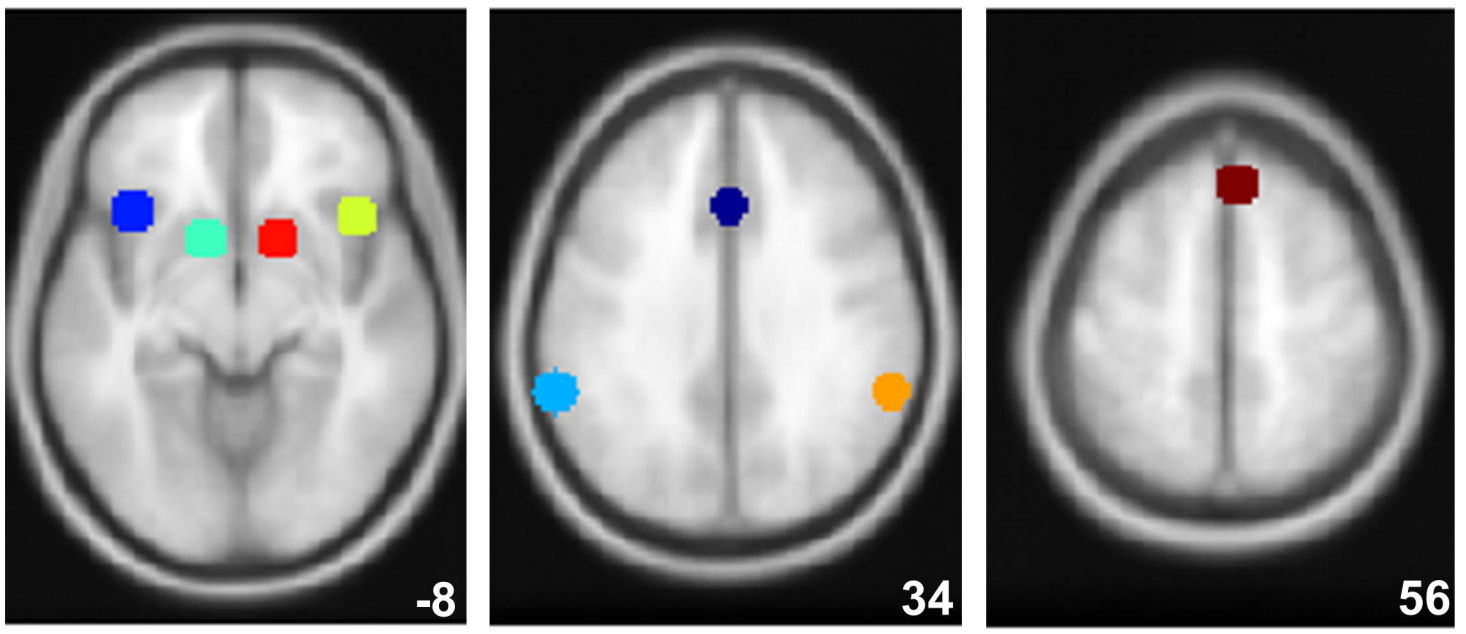

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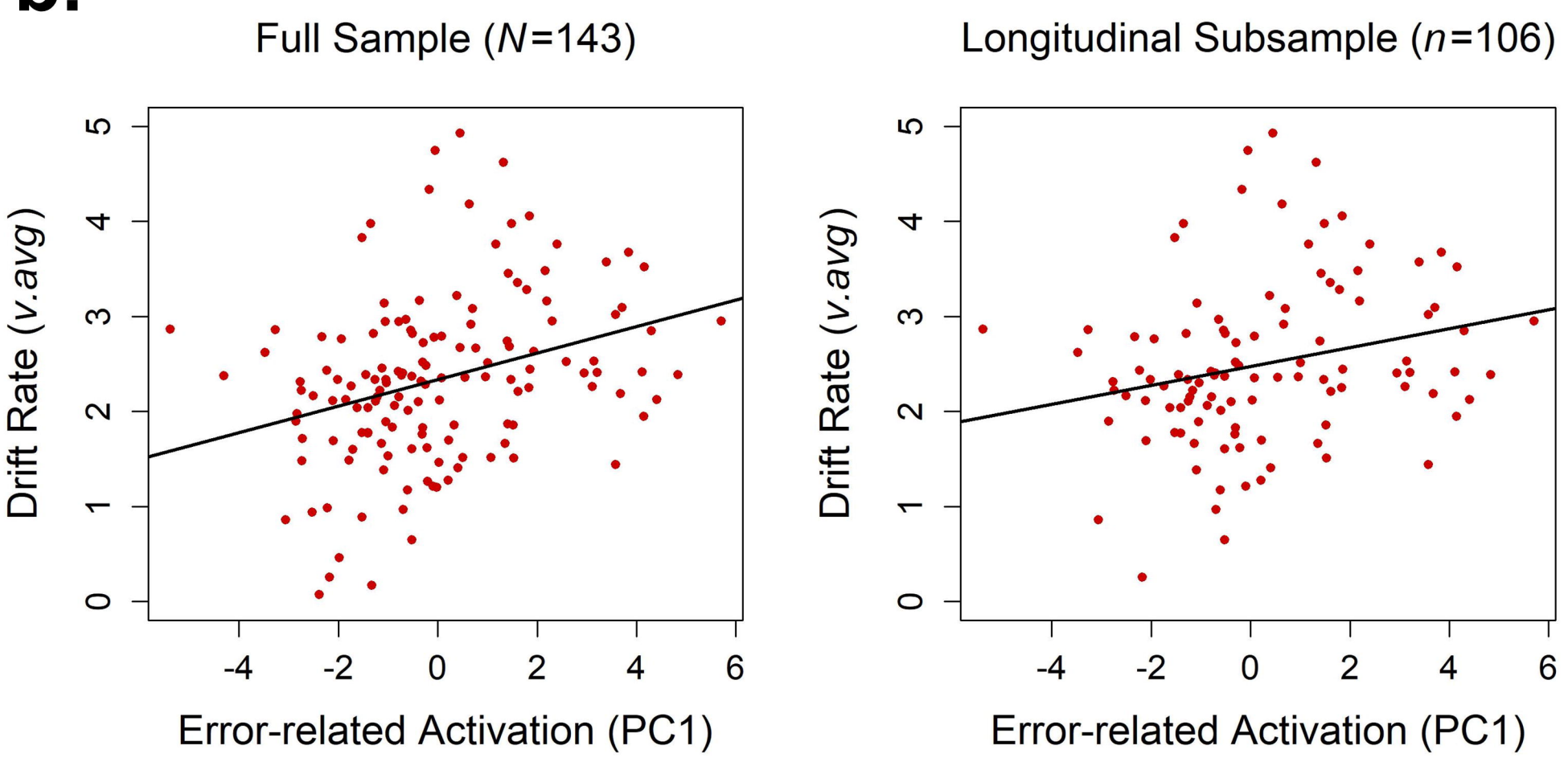

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