Assessing the influence of dopamine and mindfulness on the formation of task-relevant eye-movement patterns

A Preprint

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Abstract

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***K*eywords** blah · blee · bloo · these are optional and can be removed

```
## Loading required package: Rcpp

## Loading 'brms' package (version 2.18.0). Useful instructions
## can be found by typing help('brms'). A more detailed introduction
## to the package is available through vignette('brms_overview').

##
## Attaching package: 'brms'

## The following object is masked from 'package:stats':
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## -- Attaching packages --------------------------------------- tidyverse 1.3.2 --
## v ggplot2 3.4.0     v purrr   1.0.1
## v tibble  3.1.8     v dplyr   1.1.0
## v tidyr   1.3.0     v stringr 1.5.0
## v readr   2.1.3     v forcats 1.0.0
## -- Conflicts ------------------------------------------ tidyverse_conflicts() --
## x dplyr::filter() masks stats::filter()
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```

1 Introduction

Here goes an introduction text

2 Methods

2.1 Participants

A total of 40 participants (mean age: 24.5, sd: 5, 30 female, 10 male) were recruited using the undergraduate and paid SONA pools administered by the University of Queensland. All procedures were cleared by the University of Queensland Human Research ethics committee [2017/HE000847], and were conducted in accordance with the National Statement on Ethical Conduct in Human Research. Participants were over 18 years old, had no known neurological and psychiatric conditions (assessed by self report), and no contraindications to Levodopa, as assessed by the Levodopa safety screening questionnaire. Informed consent was obtained at the start of the first session.

2.2 Procedure

Participants attended two sessions, spaced approximately 1 week apart. After initial blood pressure and mood assessments, participants received either placebo (vitamin C) or Levodopa (Madopar 125: 100 mg Levodopa and 25 mg Benserazide Hydrochloride), crushed and dispersed in orange juice, now referred to as the 'placebo' and 'DA' sessions respectively. The solution was prepared by an experimenter who did not administer the remaining experimental procedures. This protocol was sufficient to achieve double blinding in previous work (**chowdhuryDopamineModulatesEpisodic2012?**; **chowdhuryDopamineRestoresReward2013?**). Participants then completed the Five Facet Mindfulness Questionnaire (**baerUsingSelfReportAssessment2006?**) and the Barratt Impulsivity Scale [BIS; (**pattonFactorStructureBarratt1995?**)], as trait impulsivity scores are associated with midbrain dopamine D2/D3 receptor availability. Around 30 minutes after drug administration, participants completed a second blood pressure and mood rating assessment. Participants then completed the practice stage of the task, so that the experimental stage began approximately 40 minutes after drug ingestion, within the window of peak plasma availability. At the end of the session, participants completed the final blood pressure and mood rating assessment and were asked whether they thought they had been given the active or placebo drug.

2.3 Apparatus

The experimental task was run with custom code[1], written using Matlab 2012b (32 bit) and Psychtoolbox v3.0.14, on a Windows 7 (64-bit) on a Dell Precision T1700 desktop computer, displayed using a ASUS VG248 monitor. Gaze coordinates (x, y) were sampled at 120 Hz using a monitor-mounted iView Red-m infrared eye tracker (SensoMotoric Instruments GmbH, Teltow, Germany). Participants were seated from the monitor at an approximate viewing distance of 57 cm, and positioned on a chin-rest for the duration of the task.

2.4 Experimental Task

Each trial began with a fixation dot presented centrally on a grey screen [RGB: 200 200 200]. Participants were instructed to fixate on the dot to begin a trial. After 1000 ms of continuous correct fixation samples (within 100 pixels of fixation), a square was presented that comprsed 18° of degree visual angle along each length. The square could be one of four possible colours [RGBs: 87, 208, 169; 267, 145, 52; 167, 162, 229; 239, 91, 158]. After 1000 ms, a 4 x 4 grid of smaller squares appeared within the larger square, in a darker version of the background colour ([RGB]-50). Each square comprised 2.6° of visual angle. Participants were instructed that the 4 x 4 grid represented doors, and that they were to use their eyes to open the doors to find where the target was hiding. Participants were also instructed that they were to fixate on a single door to open it. When participants had fixated on a single door for over 300 ms, the door either turned black [RGB: 50, 50, 50], to denote the absence of a target, or the target was displayed and the trial was terminated. If the door had turned black, it returned to its previous colour as soon as it was detected that the participant had moved their eyes from the door. Targets were animal images drawn randomly on each trial from a pool of 100 images taken from the internet. The time at which the target was available to be found varied from trial to trial, with the onset being drawn from a uniform distribution between 500-2000 ms. Once the target was available and the correct door selected, the target was displayed for 750 ms. Upon termination of the trial, the grey screen and white fixation cross were presented (see Fig **??**A).

In each session, participants were shown two possible background and door colour sets. Participants were instructed that each colour represented a world, and that the animals had different places they preferred to

[1] `https://github.com/kel-github/variability-decision-making`

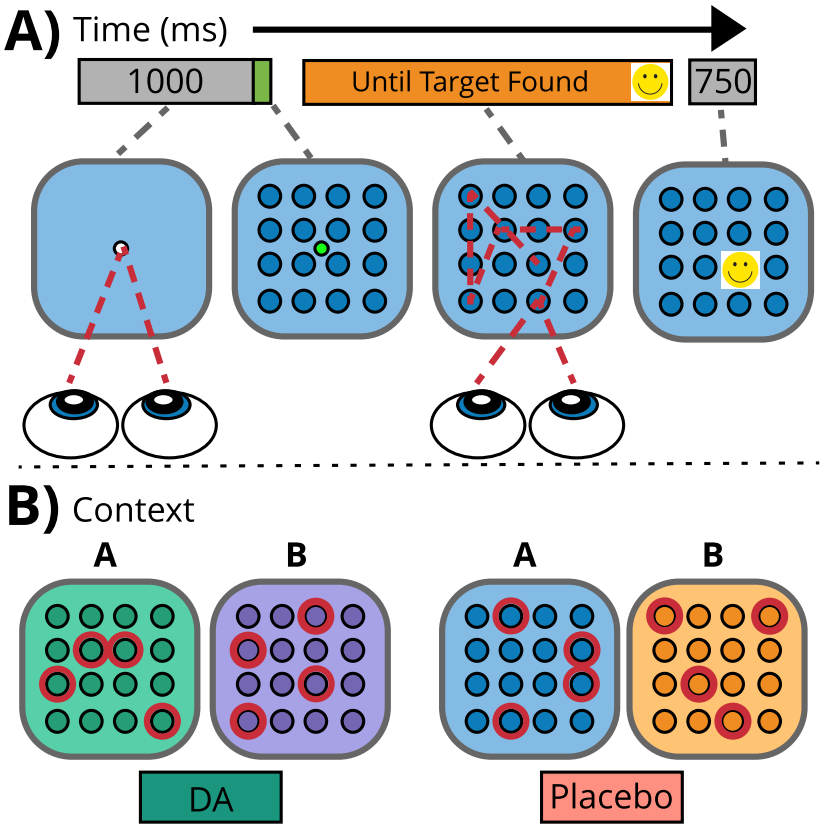

Figure 1: Experimental Task. A) A single trial where participants use their eyes to open doors to locate a target. B) Contexts and sessions: in each session, participants are exposed to two colour contexts each with 4 unique and equiprobable target locations. Colours and target locations were counterbalanced across participants and sessions. In each session, Levodopa (DA) or placebo is administered under double blind conditions.

hide, depending on the world they were in. There were four possible target locations within each world, or from here on, visual context. For each visual context, 1 door from each quadrant was selected as one of the 4 target locations where the targets could appear (see Fig **??**B), with the constraint that target locations could not overlap between contexts. Thus each colour reflected a context in which participants could establish a set of task-relevant eye-movements, i.e. towards the 4 possible target locations for that context. Note that within each context, the target was equally likely to appear behind any one of the 4 target doors (p=.25) and would never appear behind the remaining doors (p=0). Colour-target location mappings were counterbalanced across participants, as was the assignment of coloured contexts to sessions. Participants completed 80 trials in each context. Eye-movement calibration and validation was performed every 20 trials. Participants were also shown the standard QWERTY keyboard and were instructed that they could press 'x' at any time to perform a new calibration and validation if they felt that their eye-movements were no longer being registered accurately; i.e. if they were unable to open doors even though they were selecting them.

2.5 Statistical Approach

The analysis was designed to assess the learning of the target locations given the context, the extent to which eye-movements became stereotypical, and how both of these measures were modulated by the dopamine and mindfulness factors. All custom analysis code is available online[2]. The analysis was performed using R and RStudio v2022.07.2 (**rstudiocitation?**), and can be reproduced in the Neurodesk container environment (**rentonNeurodeskAccessibleFlexible2022?**).

[2]insert link

2.5.1 Data cleaning

Doors were marked as selected if participants gazed at them for a duration of at least 300 ms. We assumed that a door could not be selected twice consecutively, and collapsed any consecutive selections into a single door selection. Last, as the final door selection of every trial was fixed (i.e. finding the target location ends the trial), we removed the final selection from each trial for the sequence analysis defined below. We excluded data from one participant whose total number of door selections was greater than 3 standard deviations from the mean across both sessions. The remaining 39 datasets were retained for all of the analyses. Note that this is more inclusive than our pre-registered plan for data exclusions[3]. Based on pilot data, we had planned to exclude participants who scored $< 65\%$ accuracy over the course of a session. Analysis of the final sample suggested that this was too stringent, as this resulted in the exclusion of 14 of 40 participants.

2.6 Accuracy

We first sought to determine the extent to which participants learned the target locations, and then whether participants learned to select the doors that were relevant given the current context. Door selections were classified as target relevant (TR) for the current context (cc), the other context from that session (oc), or neither (n). Data was then grouped into blocks of 10 trials per context, and grouped across contexts, resulting in 8 blocks of 20 trials. First, to determine whether participants learned the target locations, regardless of context, we computed accuracy as the number of times participants selected a target door (referred to from now as accuracy [acc]), relative to all door selections:

$$acc = \frac{\sum (TR_{cc}, TR_{oc})}{\sum (TR_{cc}, TR_{oc}, n)}$$

We assessed the influence of block, drug and mindfulness on accuracy using a Bayesian mixed model approach. Accuracy was assumed to be drawn from a binomial distribution (1=target door, 0 = non-target door). The probability of drawing a target-door from the total number of door selections made by a given participant was modelled logistic regression. Note that as we use logistic regression, resulting regression parameter values reflect changes to the log-odds of target door selections.

For this and following analyses, we found the model that best fit the data, and made inference over the resulting parameters. We report the 95% confidence intervals (CIs) of the parameter posteriors, and assume we have detected a reliable effect when the 95% CIs of the posterior do not include zero. Models were fit using the BRMS (**burknerBrmsPackageBayesian2017?**) interface for Stan (**standevelopmentteamStanModelingLanguage?**) and RStan (**standevelopmentteamRStanInterfaceStan2023?**). We used the default weakly informative priors as specified in (**burknerBrmsPackageBayesian2017?**). Specifically, fixed and random effect β coefficients were given a flat prior, intercept and standard deviations were assumed to be drawn from a student's t distribution (df=1, location=0, scale=2.5), and the LKJ-correlation prior with parameter $\zeta > 0$ was used for the parameter covariance matrix. For each model, we checked for parameter recovery using simulated data. Once fitted, we checked that the residuals showed no signs of systematic error, that the chains had converged, and that $\hat{R}$ values were less than 1.01.

To eschew an overly large model space, and in line with our pre-registration, we first fit models that contained each possible combination of the block and drug regressors (and associated random effects), and found the best model using leave-one-out (LOO) cross validation (as implemented in **vehtariPracticalBayesian-Model2017?**). (Note that in the pre-registration document we had proposed to compare models using the deviance information criterion (DIC). As LOO is more robust than DIC to influential observations, and is readily implemented for use with BRMS model objects, we opted to use LOO instead of DIC). Upon identifying the best model, we then added the mindfulness regressor using all possible combinations, and once again selected the best model (as evidenced by LOO). Last we controlled for trait impulsivity by adding BIS scores as a main effect to the winning model. Note that in no cases did adding BIS scores improve the model. We report the difference in the expected log posterior density (ELPD) between the next best models and the winning model, and the ratio of the ELPD difference to the standard error (SE) of the difference (ELPD:SE), thus a negative ELPD difference reflects preference for the winning model. The full set of model comparisons are presented in the supplementary materials.

[3] `https://osf.io/2y6pk`

2.7 Contextual Accuracy

We next sought to understand whether dopamine modulates the ability of participants to select the correct door, given the context. Therefore, for each context, we computed the total number of cc door selections (c-acc), and modelled the probability of attaining c-acc given the total number of correct door selections:

$$c{-}acc = \frac{\sum TR_{cc}}{\sum (TR_{cc}, TR_{oc})}$$

We then modelled this data using the Bayesian mixed effects approach described above (Note that in the pre-registration document we had suggested to include a regressor for context. Visual inspection of the data showed that c-acc was highly comparable across contexts [see supplemental figures]. We therefore opted to simplify the model space and collapse over this factor).

2.8 Stereotypical door selections

Next, we determined the extent to which door-selection patterns increased in stereotypy over the course of the task, and whether dopamine and mindfulness modulates the extent of stereotypy. Here we define stereotypy as sets of door selections being deployed in the same order, over trials (e.g. **desrochersHabitLearning-Naive2015?**). Therefore we wish to know whether, given the doors that a participant chose to open over the trials of the experiment, does their data suggest that they are selecting them in a more regularised manner as the experiment progresses?

In order to characterise the extent to which door selections increased in stereotypy, we reasoned that stereotypy should be evidenced by an increase in the probability of a subset of door selection transitions, at the expense of others. This stands in contrast to when making door selections in an exploratory, or non-stereotyped way, where a greater number of door transitions should show comparable probabilities. Therefore, the transition probability matrices of individuals engaged in more stereotypical door selections should show higher variance than those who are not engaging in stereotypical door selections. We therefore computed trial level transition probability matrices, and computed the variance of each matrix. Variances were then collapsed across context and trials to form a variance score for each participant, session and block.

The resulting variance scores were subject to a comparable Bayesian mixture modelling approach as described above with a few key differences; the variance scores were assumed to be drawn from a skewed normal distribution $\mathcal{N}(\mu, \sigma, \alpha)$ whose mean (μ) was defined by the regression parameters (the distribution of variance scores can be found in the supplemental materials). σ was assumed to be drawn from a Student's t distribution (df=3, location=0, scale=2.5), the skew parameter (α) was assumed to be drawn from a normal distribution $\mathcal{N}(0, 4)$. The remaining priors for the intercept, beta-coefficients and parameter covariance matrix were defined in the same manner as for the accuracy data models. As the log-log plot of variances vs block suggested a power function, analysis was performed on the logged data. This ensured that the relationship between block and variance values was best described by a straight line. Identification of the winning model proceeded as described for the accuracy data above.

2.9 Blinding analyses

To determine whether awareness of the dopamine intervention could have contributed to the findings, the probability of participant and experimenter ratings were compared to the expected values assuming chance guessing, using a binomial model. Blood-pressure and mood measures were compared using [insert whether paired t-test or Mann-Whitney U test].

3 Results

HERE I INSERT THE BRIEFEST OVER VIEW OF ALL THE RESULTS

3.1 Accuracy

3.1.1 Model Selection

First we sought the model with the greatest predictive accuracy so that we could make subsequent inference over the parameters. The model that best accounted for the experimental factors contained main fixed effects

of block and drug, and random effects for block x drug. Although this model was only closely preferred to the next most complex model that contained a block x drug interaction (ELPD diff = -0.17, ELPD:SE = -0.32), it was strongly preferred to all other models (min ELPD diff = -674.10, ELPD:SE = -8.35). Adding mindfulness scores improved the predictive accuracy of the model; the winning model contained an additional main effect of mindfulness, two-way interactions with block and with drug, and a 3-way block x drug x mindfulness interaction (ELPD diff = -12.02, ELPD:SE = -1.88). Adding BIS scores did not improve the predictive value of the model (ELPD diff = -0.16, ELPD:SE = -0.34). Note that although we draw inferences over parameters from the winning model, our inferences are the same as if we had used the more complex model that includes the BIS scores.

3.1.2 The effect of drug and mindfulness on accuracy

Having established the best model to account for the data, we next determine the influence of DA and mindfulness on accuracy by making inference over the resulting parameters. Accuracy data plotted by block x drug session (DA va placebo) are shown in Fig 2A. Critically, the influence of drug on accuracy was impacted by mindfulness scores. The drug x mindfulness parameter differed reliably from zero (mean log odds = -0.11, 95% CI[-0.16, -0.06], see Fig 2E). To better understand this interaction, we computed a score for each participant that reflected the mean accuracy change due to the drug session (μ acc[DA - P]). Note that a positive score indicates that performance was better in the DA session relative to placebo. Next we examined the relationship between drug-induced accuracy changes and mindfulness scores. As can be seen in Fig 2B, there was a positive relationship between drug-induced accuracy changes and mindfulness; participants scoring higher for mindfulness showed higher accuracy for the DA relative to the placebo session, for example, those scoring in the highest quartile showed mean accuracy scores of 0.67 (95%CI[0.65, 0.70]) during the DA session, relative to mean accuracy scores of 0.62 (95% CI[0.60, 0.63]) during the placebo session. Individuals scoring low on mindfulness showed the opposite pattern (DA mean accuracy = 0.61, 95% CI[0.60, 0.63], placebo mean accuracy = 0.68, 95%CI[0.66, 0.69]), note that Fig 2B shows the difference between these accuracy scores). Thus the impact of DA on the establishment of task-relevant eye-movements is dependent on the mindfulness state of the individual.

Participants learned the target door locations over the course of the sessions, accuracy reliably increased over blocks. Mean accuracy in block 1 was 0.57 (95% CI[0.55, 0.59]), relative to a block 8 mean of 0.70 (95% CI[0.68, 0.72]). The model showed that accuracy increased by block with an average log odds of = 0.15, (95% CI[0.09, 0.22, Fig 2C). There was also the suggestion of a main effect of the drug intervention (mean log odds = 0.04, 95% CI[-0.001, 0.09, Fig 2D), however, the impact of drug on accuracy is presumably better explained by the drug x mindfulness interaction.

3.2 Contextual accuracy (acc)

3.2.1 Model Selection

The model that best accounted for the experimental factors contained main fixed effects of block and drug, and random effects for block x drug. Although this model was only closely preferred to the next most complex model that contained a block x drug interaction (ELPD diff = -0.66, ELPD:SE = -1.67), it was strongly preferred to all other models (min ELPD diff = -553.79, ELPD:SE = -8.35). Adding mindfulness scores improved the predictive accuracy of the model; the winning model contained an additional main effect of mindfulness (ELPD diff = -0.13, ELPD:SE = -0.12). Adding BIS scores did not improve the predictive value of the model (ELPD diff = -0.02, ELPD:SE = -0.03). Note that although we draw inferences over parameters from the winning model, our inferences are the same as if we had used the more complex model that includes the BIS scores.

3.2.2 Drug, and not mindfulness, impacts contextual accuracy

Having established the best model to account for the data, we next determined the influence of DA and mindfulness on accuracy by making inference over the resulting model parameters (see Fig 3. DA reduced contextual accuracy; accuracy was on average 0.64 (95% CI [0.63, 0.65]) for the DA session, and 0.66 (95% CI [0.65, 0.68]) for the placebo session. The log-odds of selecting a target door that was specific to the current context increased by (mean log odds = 0.07, 95% CI[0.01, 0.13, Fig 3A&B) for the placebo session, relative to the DA session.

Participants learned to make contextually accurate door selections over the course of the sessions; Mean accuracy in block 1 was 0.59 (95% CI[0.58, 0.61]), relative to a block 8 mean of 0.69 (95% CI[0.67, 0.71]).

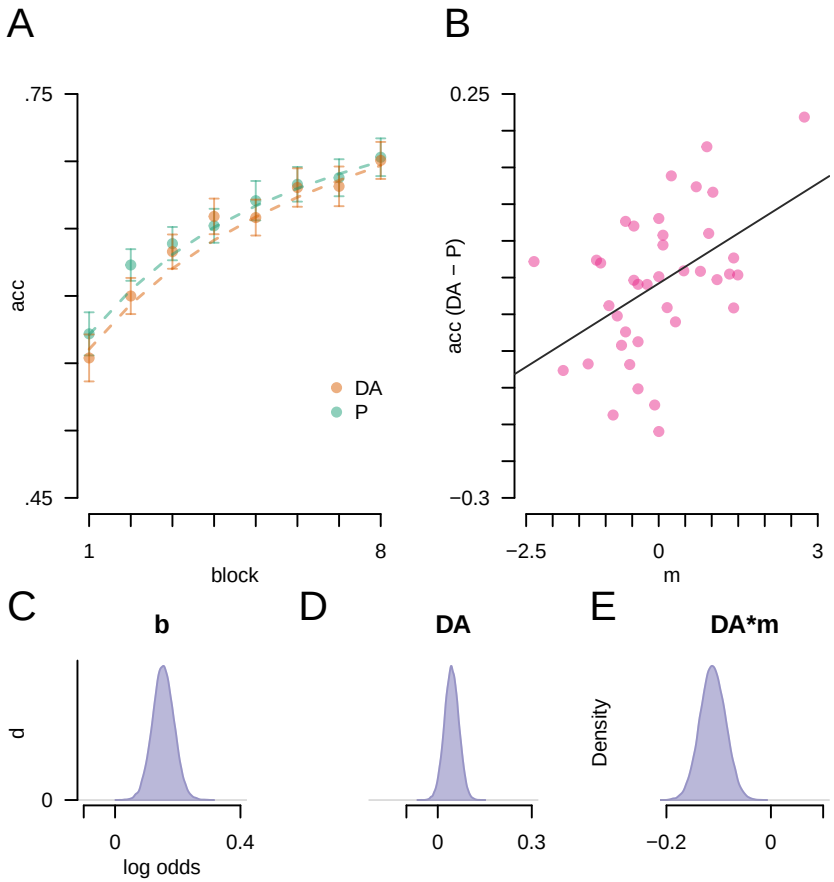

Figure 2: The influence of dopamine and mindfulness on accuracy. A) Accuracy (acc) data by block and drug. Circles reflect observed average accuracy, dotted lines reflect the fit of the winning model. B) The association between trait mindfulness (x-axis) and the impact of drug on accuracy [DA-P]. The bottom row shows posterior densities (in log odds) estimated for C) the main effect of block (b), D) the main effect of DA, and E) the drug x mindfulness (m) interaction. DA = dopamine, P = placebo, d = density. Error bars reflect within-subject standard error of the mean [SE].

The model showed that contextual accuracy increased by a mean log odds of 0.13 (95% CI[0.07, 0.19) over each block (Fig 3C). In contrast to the overall accuracy data, mindfulness did not have a reliable impact on contextual accuracy (mean log odds = 0.04, 95% CI[-0.04, 0.15]).

3.3 Stereotypy of door selections

3.3.1 Model Selection

The model that best accounted for the experimental factors contained main fixed effects of block and drug, and random effects for block x drug. Although this model was only closely preferred to the next most complex model that contained a block x drug interaction (ELPD diff = -0.26, ELPD:SE = -1.29), it was strongly preferred to all other models (min ELPD diff = -130.14, ELPD:SE = -7.71). Adding mindfulness scores improved the predictive accuracy of the model; the winning model contained an additional main effect of mindfulness and a drug x mindfulness interaction (ELPD diff = -3.15, ELPD:SE = -0.92). Adding BIS scores did not improve the predictive accuracy of the model (ELPD diff = -0.54, ELPD:SE = -1.41). Note that although we draw inferences over parameters from the winning model, our inferences are the same as if we had used the more complex model that includes the BIS scores.

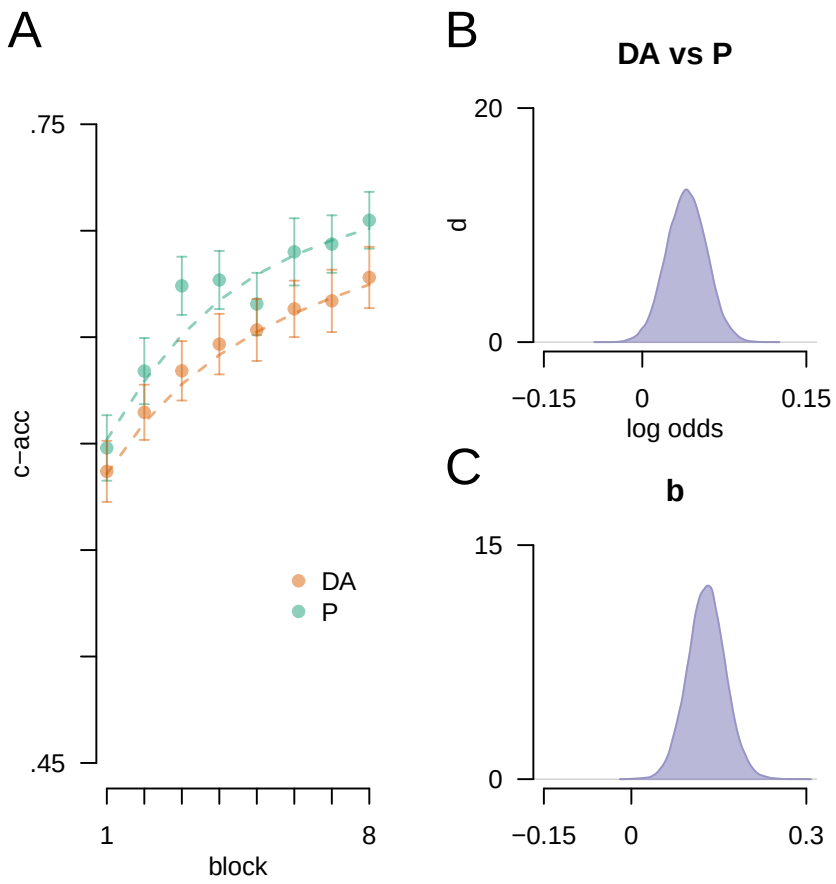

Figure 3: The influence of dopamine and mindfulness on contextual accuracy. A) Accuracy (acc) data by block and drug. Circles reflect observed average accuracy, dotted lines show the fit of the winning model. B) Estimated posterior density (in log odds) for the main effect of drug (DA vs P), D) same as in B, but for the main effect of block. DA = dopamine, P = placebo, b = block, d = density. Error bars reflect within-subject standard error of the mean [SE].

3.3.2 The impact of drug and mindfulness on stereotypy

In line with the notion that mindfulness and dopamine interact to impact the formation of stereotypical door selections, we observed a reliable drug x mindfulness interaction (mean $\beta = 0.11$, 95% CI[0.02, 0.21, Fig **??**X). Participants scoring higher for mindfulness showed lower stereotypy for the DA relative to the placebo session, for example, those scoring in the highest quartile showed mean log variance scores of -8.74 (95%CI[-8.80, -8.68]) during the DA session, relative to mean log variance scores of -8.68 (95% CI[-8.74, -8.62]) during the placebo session. Individuals scoring low on mindfulness (lowest quartile) showed the opposite pattern (DA mean accuracy = -8.69, 95% CI[-8.75, -8.63], placebo mean accuracy = -8.72, 95%CI[-8.78, -8.66]). To visualise this interaction, we computed a mean variance change score between drug sessions for each participant (μ acc[DA - P]). Note that a positive score indicates that performance was better in the DA session relative to placebo. As can be seen in Fig **??**X, there was a negative relationship between drug-induced variance changes and mindfulness.

Thus the impact of DA on the establishment of task-relevant eye-movement sequences is dependent on the mindfulness state of the individual.

LaTeX command can be used to reference other section. See Section **??**. However, you can also use **bookdown** extensions mechanism for this.

3.4 Headings: second level

You can use equation in blocks

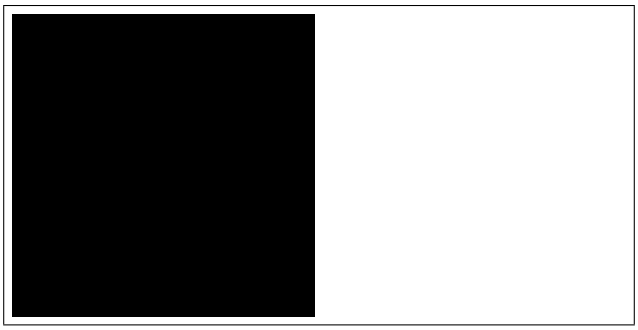

Figure 4: Sample figure caption.

$$\xi_{ij}(t) = P(x_t = i, x_{t+1} = j|y, v, w; \theta) = \frac{\alpha_i(t) a_{ij}^{w_t} \beta_j(t+1) b_j^{v_{t+1}}(y_{t+1})}{\sum_{i=1}^{N} \sum_{j=1}^{N} \alpha_i(t) a_{ij}^{w_t} \beta_j(t+1) b_j^{v_{t+1}}(y_{t+1})}$$

But also inline i.e $z = x + y$

3.4.1 Headings: third level

Another paragraph.

4 Examples of citations, figures, tables, references

You can insert references. Here is some text (Kour and Saabne 2014b, 2014a) and see Hadash et al. (2018).
The documentation for `natbib` may be found at
You can use custom blocks with LaTeX support from **rmarkdown** to create environment.

`http://mirrors.ctan.org/macros/latex/contrib/natbib/natnotes.pdf%7D`

Of note is the command `\citet`, which produces citations appropriate for use in inline text.
You can insert LaTeX environment directly too.

```
\citet{hasselmo} investigated\dots
```

produces

> Hasselmo, et al. (1995) investigated...

`https://www.ctan.org/pkg/booktabs`

4.1 Figures

You can insert figure using LaTeX directly.
See Figure 4. Here is how you add footnotes. [^Sample of the first footnote.]
But you can also do that using R.
You can use **bookdown** to allow references for Tables and Figures.

4.2 Tables

Below we can see how to use tables.
See awesome Table~1 which is written directly in LaTeX in source Rmd file.

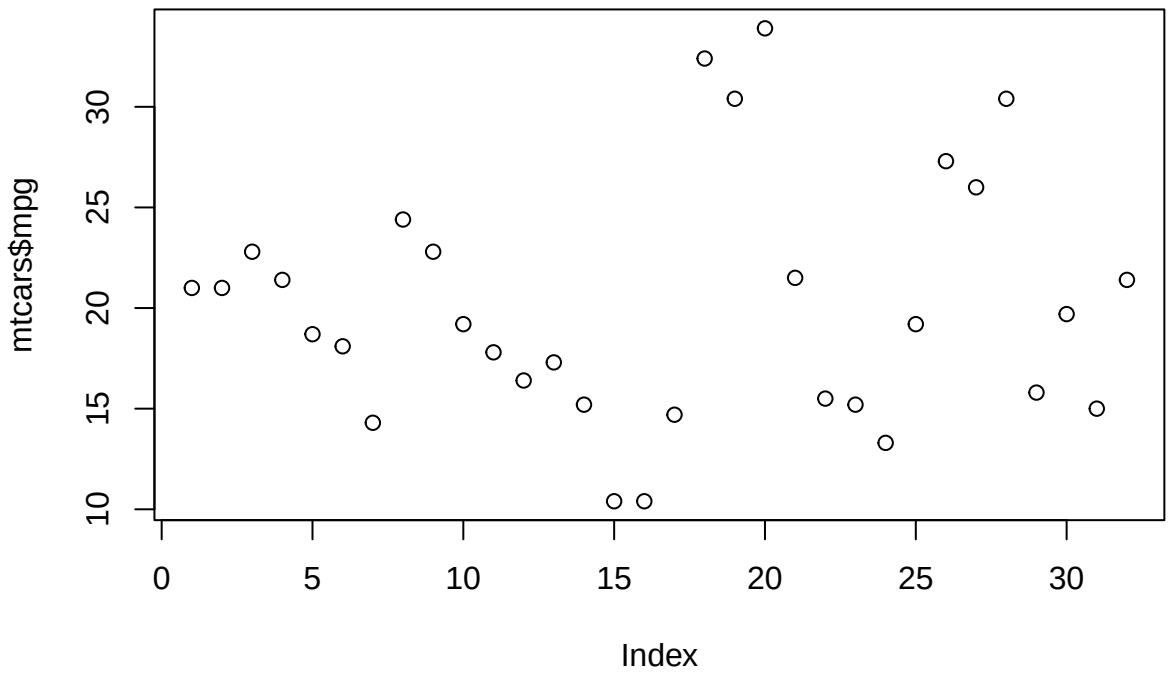

Figure 5: Another sample figure

Table 1: Sample table title

Part		
Name	Description	Size (μm)
Dendrite	Input terminal	$\sim$100
Axon	Output terminal	$\sim$10
Soma	Cell body	up to 10^6

You can also use R code for that.

Table 2: Head of mtcars table

	mpg	cyl	disp	hp	drat	wt	qsec	vs	am	gear	carb
Mazda RX4	21.0	6	160	110	3.90	2.62	16.5	0	1	4	4
Mazda RX4 Wag	21.0	6	160	110	3.90	2.88	17.0	0	1	4	4
Datsun 710	22.8	4	108	93	3.85	2.32	18.6	1	1	4	1
Hornet 4 Drive	21.4	6	258	110	3.08	3.21	19.4	1	0	3	1
Hornet Sportabout	18.7	8	360	175	3.15	3.44	17.0	0	0	3	2
Valiant	18.1	6	225	105	2.76	3.46	20.2	1	0	3	1

4.3 Lists

- Item 1
- Item 2

- Item 3

Hadash, Guy, Einat Kermany, Boaz Carmeli, Ofer Lavi, George Kour, and Alon Jacovi. 2018. "Estimate and Replace: A Novel Approach to Integrating Deep Neural Networks with Existing Applications." *arXiv Preprint arXiv:1804.09028*.

Kour, George, and Raid Saabne. 2014a. "Fast Classification of Handwritten on-Line Arabic Characters." In *Soft Computing and Pattern Recognition (SoCPaR), 2014 6th International Conference of*, 312–18. IEEE.

———. 2014b. "Real-Time Segmentation of on-Line Handwritten Arabic Script." In *Frontiers in Handwriting Recognition (ICFHR), 2014 14th International Conference on*, 417–22. IEEE.