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Cannabinoids Disrupt Memory Encoding by Functionally Isolating Hippocampal CA1 from CA3

--Manuscript Draft--

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Abstract:	Much of the research on cannabinoids (CBs) has focused on their effects at the molecular and synaptic level. However, the effects of CBs on the dynamics of neural circuits remains poorly understood. This study aims to disentangle the effects of CBs on the functional dynamics of the hippocampal Schaffer collateral synapse by using data-driven nonparametric modeling. Multi-unit activity was recorded from rats doing a working memory task in control sessions and under the influence of exogenously administered tetrahydrocannabinol (THC), the primary CB found in marijuana. It was found that THC left firing rate unaltered and only slightly reduced theta oscillations. Multivariate autoregressive models, estimated from spontaneous spiking activity, were then used to describe the dynamical transformation from CA3 to CA1. They revealed that THC served to functionally isolate CA1 from CA3 by reducing feedforward excitation and theta information flow. The functional isolation was compensated by increased feedback excitation within CA1, thus leading to unaltered firing rates. Finally, both of these effects were shown to be correlated with memory impairments in the working memory task. By elucidating the circuit mechanisms of CBs, these results help close the gap in knowledge between the cellular and behavioral effects of CBs.
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Question	Response
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Cannabinoids Disrupt Memory Encoding by Functionally Isolating Hippocampal CA1 from CA3

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Research into cannabinoids (CBs) over the last several decades has found that they induce a large variety of oftentimes opposing effects on various neuronal receptors and processes. Due to this plethora of effects, disentangling how CBs influence neuronal circuits has proven challenging. This paper contributes to this by using data driven modeling to examine how THC affects the input-output relationship in the Schaffer collateral synapse in the hippocampus. It was found that THC functionally isolated CA1 from CA3 by reducing feedforward excitation and theta information flow while simultaneously increasing feedback excitation within CA1. By elucidating the circuit mechanisms of CBs, these results help close the gap in knowledge between the cellular and behavioral effects of CBs.

The use of sophisticated computational and system identification techniques to interpret complex biological datasets makes this paper ideally suited for PLOS Computational Biology. Furthermore, a central theme in the paper is that such techniques can offer neuroscientists greater insight than more conventional techniques. We make an effort to directly compare these techniques in the paper.

Response to Reviewers (2nd round)

1. Figure 1A - The in-text version (but not the version added to the end of the manuscript) has an incorrect legend, with Control and THC labels swapped for green and blue legend lines.

RESPONSE: this has been corrected

2. Line 287-288. The reviewer concurs that Lee et al (and others) have not proven connections from pyramidal cells to CCK+ basket cells do not exist. They may very well exist. However, while evidence has been published of many other connections from pyramidal cells to other interneuron types, this reviewer has not seen any for direct monosynaptic connections from pyramidal cells to CCK+ basket cells, and it does not appear to be for lack of trying (across many articles, not just the small study of Lee). This reviewer hopes to be proven wrong, and if so, please include the citation in this paragraph (that includes line 287-288). But if the authors are not aware of any experiments either, they should consider stating such or removing the word "basket" to say "We hypothesize that this is due to reduced feedback inhibition from CA1 cholecystokinin (CCK)-containing cells" or be prepared to receive this criticism from readers after publication.

RESPONSE: This is a good point and the reviewer's suggestion was adopted: the word 'basket' was removed.

Thanks!

3. [Minor] The word "amount" is still sometimes used for countable quantities in this text, where it would be clearer to say "number"

RESPONSE: this has been corrected 4 times in the text. Thank you for pointing this out

Reviewer #3: This paper nicely describes the effects of cannabinoids on the systems-level of network information transfer between rat CA3 and CA1 and the association with a measure of impaired memory encoding under the drug. The approach is fairly novel based on strong expertise of the authors using statistical modeling of spike input-output relationships. Their findings are interesting in finding no significant differences in firing rates in CA3 and CA1 under drug and more importantly, finding significant excitatory and inhibitory principle components that correlate with memory impairment. Some further considerations....

1. In fig. 1a, I see the 12% decrease in correct choices. If you consider 50% as chance, then it seems more like a 24% impairment. Does this better match your 20% loss of inhibition in your model?

RESPONSE: This is a good point. We have modified lines 90-91 to read: "On the behavioral level, it was found that THC reduced rodent-performance on the DNMS task by about 12.2+-6% (Fig. 1a). This corresponds to a 24.4% impairment relative to baseline performance at 50%."

2. In Fig 1e, is it worth noting that the peak of the difference is at a lower frequency than the peaks of the power spectrum?

RESPONSE: This is a good point. The following sentence has been added to the text: "Interestingly, in both cases, the significant reduction of theta power occurred at 5-6Hz, which is lower than the observed theta peak. "

The authors have reasonably responded to the prior reviewers' comments.

Very minor points

Fig 1c, *** is not defined.

RESPONSE: This has now been defined in the caption (*=P<.001)**

In Methods, line 301, who made the electrode array and what are its characteristics? Number of shanks, spacing, electrodes/shank, spacing.

RESPONSE: This information is in the supplemental information under surgery: "Craniotomies (5mm-diameter) were performed bilaterally over the dorsal hippocampus to provide for implantation of 2 identical array electrodes (Neurolinc, New York, NY), each consisting of two rows of 8 stainless steel wires (diameter: 20 µm) positioned such that the geometric center of each electrode array was centered at co-ordinates 3.4 mm posterior to Bregma and 3.0 mm lateral (right or left) to midline [66]. The array was designed such that the distance between two adjacent electrodes within a row was 200 µm and between rows was 400 µm to conform to the locations of the respective CA3 and CA1 cell layers."

Reviewer #1: The authors have applied a novel analysis and interpretation to a study of the effects of THC on behavioral and cellular activity in rats. Based on a decrease in the efficacy and theta modulation of CA3 output to CA1, along with a lack of effect on theta modulation and firing rates in CA1 cells, the authors propose that the two subfields become less coupled when under the influence of THC and suggest that this reaction may explain the behavioral deficits seen in the delayed non-match to sample task when performed by rats under the influence of THC. This interpretation has potential and would be a valuable addition to the literature if it is found to be true. However, it is inconsistently explained and supported within this manuscript, and a part of it is based on incorrect assumptions about CA1 anatomical connectivity. There are concerns in terms of science and writing quality that must be addressed for this work to present a compelling case for its analysis and interpretation.

General Comments: This reviewer has raised excellent points relating to the mismatch between our hypothesis and the current literature. These comments were extremely helpful and have inspired us to review the current literature much more carefully. Thus, we have completely rewritten the paragraph dealing with our proposed hypothesis in the discussion. The new paragraph is found on 286-329. Whether this manuscript will ultimately be accepted in PLOS Computational Biology or not, we are very grateful to this reviewer for helping us make our work much stronger.

Scientific Concerns:

1. Results - Manuscript Page 7, lines 186 - 188: "This confirms previous reports which show ... that CA1 is capable to generating endogenous theta rhythms". It is consistent with the report of Goutagny et al 2009 but does not confirm it - CA1 also receives timed input from sources other than CA3 (ECIII and medial septum are two of the most significant), and there is no reason to discount their input here when the authors have not shown any effect of THC on their spike timing or theta modulation.

Response: This is a valid point. Septal inputs to the hippocampus are particularly important for theta rhythms (for example, see Fuhrmann et al., 2015; Neuron). The language has been made more precise to reflect this: "**This is consistent with previous reports which show that CA3 propagates strong theta rhythms to CA1 [39,40] and also that CA1 is capable to generating endogenous theta rhythms [41].**"

2. Discussion - Manuscript Page 10, lines 295-303. The authors first refer to "increased feedback excitation" but the proposed mechanism given below sounds more like "decreased feedback inhibition" and even includes a contributing factor of decreased CA1 pyramidal input to the inhibitory cells, so the proposed mechanisms are not consistently described or represented throughout the discussion. Relatedly, in the results section (Manuscript page 7, lines 211-212), the authors state "Essentially, the more THC increased feedforward inhibition and feedback excitation, the worse the rodent did on the task", which is also confusing as elsewhere the authors seem to indicate that the feedforward inhibition (anatomically, this should be the CCK+ cell activity) is weakened with THC.

Response: This remark is very helpful. Indeed, the system identification method was able to detect a change in feedback excitatory index in CA1, but it is agnostic as to whether that is caused by reduced feedback inhibition or increased feedback excitation. As the reviewer points out, we hypothesize that it is the former. To make this point more clear, we changed the discussion to read: "**It was found that THC increased feedback excitatory index in CA1 and that the magnitude of this effect was correlated with behavioral deficits. We hypothesize that this is due to reduced feedback inhibition from CA1 cholecystokinin (CCK)-containing basket cells. ...**" Furthermore, the sentence which mentioned increased feedback excitation in the results section was completely removed.

3. Discussion - Manuscript page 10, line 300-301 states in regard to CCK+ cells that "their primary input and output is from/to CA1 pyramidal 301 cells [52]." It is true their primary output is to CA1 pyramidal cells, however it is misleading to state that their primary input is from CA1 pyramidal cells. Reference #52 does not make that claim, speaking only to the proportion of CA1 inputs for all interneuron types together, and in fact this reviewer is not aware of any definitive published evidence for monosynaptic connections from CA1 pyramidal cells to CCK+ basket cells, although there are known connections from CA1 pyramidal cells to other CCK+ cells. It would be more correct to state "their primary output is CA1 pyramidal cells and some types of CCK+ cells also receive input from CA1 pyramidal cells" as shown for example in **Lee et al J Neurosci 2010**.

Response: This point is answered together with point 4 below

4. It follows that the statement "(2) reducing their total amount of action potentials due to reduced glutamatergic input from CA1 pyramidal cells" is probably untrue for CCK+ basket cells, which are the majority of CCK+ cells in CA1. Most CCK+ cells have dendrites in the area of Schaffer Collateral innervation of CA1 and are activated by the afferent Schaffer Collateral input (although some have dendrites within the oriens where most CA1 pyramidal cell collaterals would be found), so a reduction in afferent SC input is far more likely to be responsible for reduced drive to CCK+ cells than a reduction in CA1 pyramidal input and in the case of CCK+ basket cells, this is especially true.

Response: We thank the reviewer for bringing these points to our attention. After looking at the literature more closely we agree that the primary input to CA1 CCK basket cells comes from CA3 rather than CA1 pyramidal cells (Lee et al., 2010; Matyas et al., 2004). Matyas et al., 2004 also showed that 20% of CA1 CCK cells' inputs are in the str. oriens

layer and suggested that these inputs are from CA1 pyramidal collaterals¹. In either case, as the reviewer pointed out, our theory is valid whether the decreased excitatory input comes from CA3 or CA1 pyramidal cells. Both have the net effect of reducing CA1 CCK basket cell activity and thus CA1 feedback inhibition. Thus, we have changed the relevant sentence to: “While CCK cells only make up 13.9% of interneurons (Bezaire et al., 2013), they express significantly more CB1 receptors than any other cell in the hippocampus (Katona et al., 2000), and their primary output is to CA1 pyramidal cells. Increased THC concentrations would reduce CCK interneuron output by (1) reducing the amount of GABA they release per action potential (2) reducing their MFR due to reduced glutamatergic input from principal cells in both CA3 and CA1.”

5. Manuscript Page 10, line 299 - “they express significantly more CB1 receptors than any other cell in the hippocampus [53],” but not all CB1 receptors are created equal; those found on pyramidal cells are thought to be **more** efficacious, so it would be helpful to consider this in addition to the receptor abundance. It would also be helpful to discuss the roles of DSI and DSE in the circuit and the effect of THC on those roles. For background on this and the previous point, check out Ruehle et al J Psychopharmacology 2012 and the references it cites.

Response: We are very grateful that the reviewer brought these sources to our attention. We have elaborated on the point that pyramidal cell CB1 receptors are more efficacious in our discussion: “Even though pyramidal cells have much lower densities of CB1 receptors than interneurons (Katona et al., 2000; Oshno-Shosaki et al., 2002), there is evidence that CB induced reduction of excitation is larger than these relative densities suggest. Principal cells outnumber interneurons 20:1 in CA1 (Ahmed and Mehta, 2009) and their CB1 receptors were found to be several fold more efficacious than those of interneurons (Steindel et al., 2009). Further, lower baseline activation levels of CB1 receptors on principal cells than on interneurons suggest they would be disproportionately activated by CB agonists (Ruehle et al., 2012).”

Writing & readability concerns

The writing level of this manuscript **occasionally** falls below what this reviewer would expect and distracts from the scientific message. It is very fixable. This reviewer recommends:

1. Before revising the manuscript, (re)read a short book on writing or scientific writing. Style: Basics of Clarity and Grace by Joseph Williams is short and very helpful
2. Revise the manuscript, checking especially for the following (only a few examples of each problem are listed here):
 - 2a. The nouns and verbs should be appropriately plural or singular
 - 2ai. Example: Actual Page 9, line 15: synapse should be plural (synapses)
 - 2aii. Example: Manuscript Page 2, line 72-73: “... a type of linear nonparametric models ...” → models should be singular (model)
 - 2aiii. Example: “the emergent effects ... is “ → is should be plural (are)
- 2b. Keep in mind whether something is countable when deciding between using ‘amount’ and some form of ‘number’
- 2bi. Example: Manuscript page 10, line 289 - “THC reduces the amount of casually connected CA3-CA1 290 neuronal pairs”; amount → number, frequency, incidence

Response: We are deeply embarrassed by this and have done our best to improve the language, including reading the paper several times over and getting feedback from several native English speaking peers. All the above examples have been corrected according to the reviewer’s suggestions. We thank the reviewer for bringing them to our attention.

- 2c. The word ‘this’ should rarely stand alone in scientific publications - it is vague and confusing. Better to specify what it means each time
- 2ci. Manuscript Page 1, line 35: “This paper contributes to this by using” → first this (“This paper”) is good. Second one (“contributes to this”) is vague, try something like “This paper contributes to disentangling these effects by using...” which may need to be further refined to make it less awkward

Response: Sentence changed to: “This paper contributes to our understanding of the circuit level effects of CBs by using data driven modeling to examine how THC affects the input-output relationship in the Schaffer collateral synapse in the hippocampus.”

- 2cii. Manuscript Page 2, line 76: “This makes them particularly well suited” → “This characteristic makes...” or “This lack of reliance on assumptions makes ...”

Response: Sentence changed to: “This characteristic makes them particularly well suited ...”

- 2d. Remove unnecessary qualifications and rewrite unprofessional ones differently
- 2di. Example: Manuscript Page 2, line 46: “has attracted a lot of somewhat controversial attention” is distracting because of its imprecision and contrast to most writing found in journal publications

¹ Interestingly, Lee et al., 2014 did not find any evidence of direct connections from CA1 pyramidal cells to CA1 CCK basket cells; however, they had a small sample size and never implied they disproved the possibility of such connections.

Response: Sentence rewritten as “In particular, CB agonists have shown promising but mixed results in the treatment of epilepsy, as various types of agonists at various doses have been shown to be both pro- and anticonvulsant”

2e. Parallel sentence construction

2ei. Example: Manuscript Page 2, line 49: the items in this list do not follow a parallel construction, making it confusing to parse: “much work has been done on the chemical structure of various cannabinoids, cannabinoid receptors, along with their cellular interactions and pharmacology” - would be clearer as “.... on the chemical structure of various cannabinoids and cannabinoid receptors, along with their...” or “... on the chemical structure of various cannabinoids, cannabinoid receptors, and their...”

Response: Sentence changed to “Parallel to increasing therapeutic research, much work has been done on the chemical structure of various cannabinoids and cannabinoid receptors, along with their cellular interactions and pharmacology.”

2f. Word choice is not always the most appropriate

2fi. Example: Manuscript Page 10, lines 320 - 321 “the decrease in feedforward excitation overpowers the increase in feedback excitation and results in lower MFR” - it is difficult to visualize a decrease in agency overpowering something, would be more fitting to say “the increase in ... is unable to compensate for the decrease in ... , resulting in lower MFR” effect/affect

2g. Other recommendations from the writing book

3. Address these other issues as well:

3a. Manuscript page 1, lines 31-40: unclear whether this is an alternate abstract? It repeats its last sentence from the actual abstract

Response: This is a required Author Summary. A title has been added to make this more clear.

3b. Ensure transitions are appropriate - they should respect the flow of logic

3c. Spell check

3d. Appropriate use of commas. Sometimes they are extraneous, other times they are sorely needed:

3di. Example: Manuscript page 3, line 93: “While performing the DNMS task single-unit...” is confusing, add a comma to clarify: “While performing the DNMS task, single-unit...”

Response: Comma has been added.

Minor & other concerns

1. Figure 1B - what are the units on the axes? Assuming Hz for individual firing rates?

Response: Yes, that is correct. The Hz units have been added to the labels to clarify this.

2. Figure 2 caption says “Note that 1 CA1 neuron has no significant inputs.” → please specify that the statement refers to the theoretical model using Granger causality (is not intended as a biological anatomy statement based on experimental observation).

Response: Sentence changed to “Note that 1 CA1 neuron has no significant granger-causal inputs.”

3. Figure 2B could be further clarified with a “CA3 input #1” label over the CA3 spike trains, to correspond to inputs in 2C and a “CA1” label over the CA1 spike train.

Response: The figure has been modified to reflect this

4. Manuscript Page 17, line 575 is confusing: “N-1 two input models were constructed”

Response: Sentence has been changed to: “Afterwards, N-1 models were constructed with two inputs: the previously selected input and one of the remaining potential inputs.”

5. Figure 3 CD - can you add a legend for the animal colors, even if the animal names are arbitrary (“animal 1, 5 sessions; animal 2, 3 sessions; animal 3...”). It would enable readers to quickly understand the color coding w/o having to read the legend and also quickly see how many animals & sessions were included.

Response: A legend was added with the Rat 1, Rat 2, etc... The amount of sessions was added since each animal went through a certain amount of control and THC sessions. In the plots under discussion, each dot represents the difference in a value in one of the THC sessions from the mean of that value in the control sessions. Thus, I think it would be confusing to put in the amount of sessions as the reader wont know whether they refer to just the THC sessions (i.e. the # of dots of that color), or all the sessions.

6. Figure text is quite small - for example, the legend text in Figure 2C is almost unreadable

Response: All figure text was made larger.

7. There should be a short summary of the previous work, at least the categorization of functional cell types (FCTs) that currently refers to previous work for any explanation, to enable this manuscript to stand alone.

Response: This is a great point. We decided that in order to improve clarity and avoid confusion, the reference to FCTs from previous work has been removed. Instead, the paper simply refers to these cells as sample-presentation cells and provides a reference to the previous work which talked about FCTs. We believe that since this is such a minor aspect of the paper, it is preferable not to go into excessive detail on this, as it will distract the reader.

8. Figures should stand alone; spell out abbreviations in the captions (ex: Figure captions should spell out DNMS, FCT, gPDM at least once)

Response: All abbreviations in the figures have been spelled out (except for well known ones such as CA1 and THC).

9. Some references in the bibliography have corrupted characters - see reference 55 for example. Also, the journal names are not properly capitalized; if they are proper in the bib file, simply surround the whole journal title with an extra set of curly braces {} to preserve capitalization in the compiled document

Response: Corrupted characters in bibliography have been corrected, including source 55. All Journal titles have been properly capitalized.

Reviewer #2: In this paper the authors take an interesting and novel approach in applying nonparametric modelling to investigate the effect of exogenous CBS on the hippocampal Schaffer collateral synapse. In my opinion certain points (listed below) merit further clarification.

General feedback: Both this reviewer and reviewer #1 raised excellent points relating to the mismatch between our hypothesis and the current literature. In response to this, we have completely rewritten the paragraph dealing with our proposed hypothesis in the discussion. The new paragraphs are found on lines 286-329. We believe this rewritten section is much more clear and addresses the reviewer's concerns.

Comments

1. CB1 receptors are found on both excitatory and inhibitory cells in hippocampus leading to both suppression of inhibition and excitation. However, depression of inhibition is much more prevalent than the depression of excitation and can be induced with lower CB concentrations, supposedly due to the lower sensitivity of CB1 receptors expressed on excitatory rather than inhibitory synaptic terminals. (See Ohno-Shosaku, T. et al, (2002). Journal of Neuroscience and Zachariou et al 2014 Journal of Computational Neuroscience). My main concern is that this fact is not considered in the model and hypothesis formulation and in the overall results interpretation. For example in a relatively low THC dose the CB1 receptor found on excitatory terminal might not be affected. Hence, the conclusion that "THC functionally isolates CA1 from CA3 by reducing feed forward excitation and theta information flow while simultaneously increasing feedback excitation within CA1" might not necessarily hold. Please discuss/address.

Response: The reviewer's point that DSI is more prevalent than DSE is well taken. Our strongest findings pertained to changes in CA1 feedback, which we believe is due to reduced feedback inhibition from CA1 CCK basket cells (i.e. DSI). We also found evidence for reduced feedforward excitation which we believe is due to DSE. Even though DSE is less prevalent than DSI, there is evidence that in-vivo, DSE may play a more prominent role than previously thought. (this point was made by reviewer #1). We have added the following sentences to discuss this issue: "**Even though pyramidal cells have much lower densities of CB1 receptors than interneurons** (Katona et al., 2000; Oshno-Shosaki et al., 2002), there is evidence that CB induced reduction of excitation is larger than these relative densities suggest. Principal cells outnumber interneurons 20:1 in CA1 (Ahmed and Mehta, 2009) and their CB1 receptors were found to be several fold more efficacious than those of interneurons (Steindel et al., 2009). Further, lower baseline activation levels of CB1 receptors on principal cells than on interneurons suggest they would be disproportionately activated by CB agonists (Ruehle et al., 2012)."

2. The model appears to only describe excitatory cells, as it focuses on the Schaffer collateral synapse. However, in the Methods it is noted that no differentiation was made between principal cells and interneurons. How did the authors ensure that the recorded cells whose activity was considered for fitting the model were indeed excitatory?

Response: This decision was made for two reasons. First, the paper used a 'blackbox' granger-causal framework where it was understood that functionally connected cells are not necessarily anatomically connected and that the estimated feedforward/feedback filters are not physiological EPSPs but rather an abstract measure of influence. Thus, the estimated filters include not only direct neuron-to-neuron physiological processes such as dendritic integration, but also indirect processes such as feedforward inhibition whereby the recorded CA3 neuron activates an unseen CA1 interneuron which activates the recorded CA1 principal cell (Pouille and Scanziani, 2001). Given that our goal was to see how CA3 \rightarrow CA1 dynamics change with THC, and given the high levels of connectivity between CA1 pyramidal cells and interneurons, we felt that this distinction would be somewhat artificial. Second, given that we used in-vivo extracellular recordings, there is no fullproof method to separate pyramidal cells and interneurons. Commonly used methods which rely on MFR, waveform shape, and ISI distributions can only give 'putative pyramidal cells'. We attempted to use a similar procedure by removing cells with MFR >5 Hz as 'putative' interneurons. These cells made up only a minority of our recorded cells and did not significantly alter any of our results. Namely, with only 1 exception, all significant P values remained so even after these cells' exclusion (the exception was for CA3 theta power reduction on line 118 whose P value went from .045 to .062).

3. Figures: All figures would benefit from a larger font size, as currently many parts are not easily readable. In Figure 1 some axis labels and units are missing and the figure would benefit from a longer/more descriptive legend. Also I find figure 1E confusing please clarify which part shows control and which TCH (the extra y axis with THC/control is not that informative). Same holds for Figure 3A and B. In Figure 2B the y-axis is missing (and fonts are very small). Also the color-coding blue - green for control - THC should be repeated at least in every figure (and maybe in sub-figures). Also in Figure 4 each panel should be properly described.

We thank the reviewer for all these suggestions that will certainly add to the readability of the paper. The font sizes of all figures were made bigger. Axis labels and units were added in figure 1. A legend was added to Fig 1E and 3A,B. In Fig.

2, the color schema for CA3 and CA1 was changed to make it distinct from Control/THC. In Fig. 2b, the y-axis is shown for the bottom input, and the caption says that the y-axis and scale is the same for all 3 inputs. The y-axis was not added to the top two inputs for aesthetic reasons.

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1 **Cannabinoids Disrupt Memory Encoding by**
2 **Functionally Isolating Hippocampal CA1 from CA3**

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10 **Abstract**

11 *Much of the research on cannabinoids (CBs) has focused on their ef-
12 fects at the molecular and synaptic level. However, the effects of CBs on the
13 dynamics of neural circuits remains poorly understood. This study aims to
14 disentangle the effects of CBs on the functional dynamics of the hippocam-
15 pal Schaffer collateral synapse by using data-driven nonparametric model-
16 ing. Multi-unit activity was recorded from rats doing a working memory
17 task in control sessions and under the influence of exogenously administered
18 tetrahydrocannabinol (THC), the primary CB found in marijuana. It was
19 found that THC left firing rate unaltered and only slightly reduced theta os-
20 cillations. Multivariate autoregressive models, estimated from spontaneous
21 spiking activity, were then used to describe the dynamical transformation
22 from CA3 to CA1. They revealed that THC served to functionally isolate
23 CA1 from CA3 by reducing feedforward excitation and theta information
24 flow. The functional isolation was compensated by increased feedback exci-
25 tation within CA1, thus leading to unaltered firing rates. Finally, both of
26 these effects were shown to be correlated with memory impairments in the
27 working memory task. By elucidating the circuit mechanisms of CBs, these
28 results help close the gap in knowledge between the cellular and behavioral
29 effects of CBs.*

30 **Author Summary**

31 Research into cannabinoids (CBs) over the last several decades has found that
32 they induce a large variety of oftentimes opposing effects on various neuronal
33 receptors and processes. Due to this plethora of effects, disentangling how CBs
34 influence neuronal circuits has proven challenging. This paper contributes to our
35 understanding of the circuit level effects of CBs by using data driven modeling to
36 examine how THC affects the input-output relationship in the Schaffer collateral
37 synapse in the hippocampus. It was found that THC functionally isolated CA1
38 from CA3 by reducing feedforward excitation and theta information flow while
39 simultaneously increasing feedback excitation within CA1. By elucidating the
40 circuit mechanisms of CBs, these results help close the gap in knowledge between
41 the cellular and behavioral effects of CBs.

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42 1 Introduction

43 Recent years have seen a resurgence of interest in the therapeutic role of cannabinoids (CBs) for several diseases and neurophyschiatric disorders such as psychosis, anxiety disorders, PTSD, and multiple sclerosis [1, 2]. In particular, CB agonists have shown promising but mixed results in the treatment of epilepsy, as various types of agonists at various doses have been shown to be both pro- and anticonvulsant [3, 4, 5, 6, 7, 8, 7]. Parallel to increasing therapeutic research, much work has been done on the chemical structure of various cannabinoids and cannabinoid receptors, along with their cellular interactions and pharmacology [9].

52 Nonetheless, between the large bodies of literature on cannabinoids from chemical, disease, and behavioral perspectives, much less work has been done to explore the effects of cannabinoids on the neural circuit level. This is particularly important since a wide range of complex and often opposing effects have been attributed to cannabinoids on a molecular and cellular level. For example, cannabinoid activation of CB1 receptors, which are found on both pyramidal cells and interneurons, reduces the quantity of neurotransmitter released during an action potential; consequently, increased extracellular cannabinoid levels reduce both excitatory (glutamatergic) and inhibitory (GABAergic) transmission [10]. Furthermore, cannabinoids have been shown to interact with astrocytes [11], mitochondria [12], glycine receptors [13], vanilloid receptors [14], potassium ion channels [15], and to reduce GABA and glutamate reuptake [16, 17]. Consequently, it is very difficult to extrapolate the emergent network level changes simply from a catalogue of effects cannabinoids have a cellular/molecular level.

66 Here, we studied the effects of Δ^9 -tetrahydrocannabinol (THC) on hippocampal networks during memory encoding using spiking activity recorded in rodents in-vivo performing the Delayed-NonMatch-to-Sample (DNMS) working memory task. Multivariate autoregressive (MVAR) models were used in both control and THC sessions to estimate feedforward and feedback dynamical filters, which are akin to the waveform shapes of the CA3 \rightarrow CA1 EPSP and CA1 afterhyperpolarization, respectively [18]. MVAR models, which are a type of linear nonparametric model, are 'data-driven' in the sense that they estimate model parameters directly from recorded neural spiketrains and, unlike more biologically realistic models, make very few *a priori* assumptions on the nature of the neural dynamics [19, 20]. This characteristic makes them particularly well suited for this study, since as previously mentioned the emergent effects of THC on neural circuits are highly complex and unclear. Overall our results suggest that cannabinoids impair memory encoding by functionally isolating CA1 from CA3 via reduced theta information flow and altered excitatory-inhibitory balance across the Schaffer collateral synapse.

82 **2 Results**

83 **2.1 Changes in rate and temporal coding under Cannabinoids**

84 To evaluate the effects of exogenous cannabinoids on the hippocampal network
85 1 mg/kg THC was injected intraperitoneally into $N = 6$ rodents during cer-
86 tain sessions while they were performing a DNMS task (Fig. S1). All data was
87 previously used in a study on the effects of cannabinoids on hippocampal mul-
88 tifractality [21, 22]. Briefly, in the sample phase, the rats were presented one
89 of two levers. After a variable length delay, both levers were presented in the
90 match phase and the rat had to choose the opposite lever to receive a reward.
91 On the behavioral level, it was found that THC reduced rodent-performance on
92 the DNMS task by about $12.2 \pm .6\%$ (Fig. 1a, [23]). This corresponds to a 24.4%
93 impairment relative to baseline performance at 50%.

94 While performing the DNMS task, single-unit activity was recorded from the
95 hippocampal CA3 and CA1 regions using a multi-electrode array. There were no
96 significant mean firing rate (MFR) differences between THC sessions and control
97 sessions in either CA3 or CA1 cells ($P = .502$, Fig. 1b). No MFR differences were
98 seen whether considering the entire session or only times around the DNMS
99 sample phase, or whether considering all cells or only sample-presentation cells
100 (see below). The lack of any cannabinoid-induced changes in firing rates at this
101 dosage has been observed in previous studies [24, 25].

102 Two types of temporal coding were identified in the recorded spiketrains.
103 First, on slower timescales, several neurons fired preferentially in response to
104 lever presentation in the sample phase of the DNMS task [26]. It was found
105 that THC reduced the proportion of sample-presentation cells in both CA3 and
106 CA1 by roughly equal amounts ($\Delta = 13 \pm 4\%$, $P < .001$; Fig. 1c). Interestingly,
107 some sample-presentation cells lost all of their preferential firing in THC sessions
108 (Fig. 1d); this contrasts with place cells whose receptive field stays largely intact
109 under cannabinoids [27]. There was an insignificant trend connecting sample-
110 presentation cell reduction with behavioral deficits ($R^2 = .27$, $P = .052$, Fig.
111 S3a).

112 On faster timescales, it was found that several CA3 and CA1 neurons had
113 theta band rhythmicity (4-7 Hz). Hippocampal theta oscillations are known to
114 be intimately related to cognitive function [28, 29, 30] and have previously been
115 linked to performance in the DNMS task [31]; furthermore, theta oscillations are
116 known to be reduced by systemic injections of cannabinoids on both the single
117 unit [24] and network level [32]. It was found that CA1 theta power was slightly
118 but significantly reduced in THC sessions ($\Delta = 2.52\%$, $CI : [.61, 4.4]\% P = .004$;
119 Fig. 1e). A similar, albeit slightly weaker, theta power reduction was seen in
120 CA3 cells ($\Delta = 1.94\%$, $P = .045$; Fig. S2). Interestingly, in both cases, the
121 significant reduction of theta power occurred at 5-6Hz, which is lower than the
122 observed theta peak. Unlike previous results in a different task [24], the reduction
123 in CA1 theta power was not found to be correlated with behavioral deficits in
124 the DNMS task ($P = .674$, Fig. S3b).

125 Overall, these results show that THC has minor effects on the actual neuronal
126 spiketimes: quantity of spikes (MFR) was not affected and spike rhythmicity

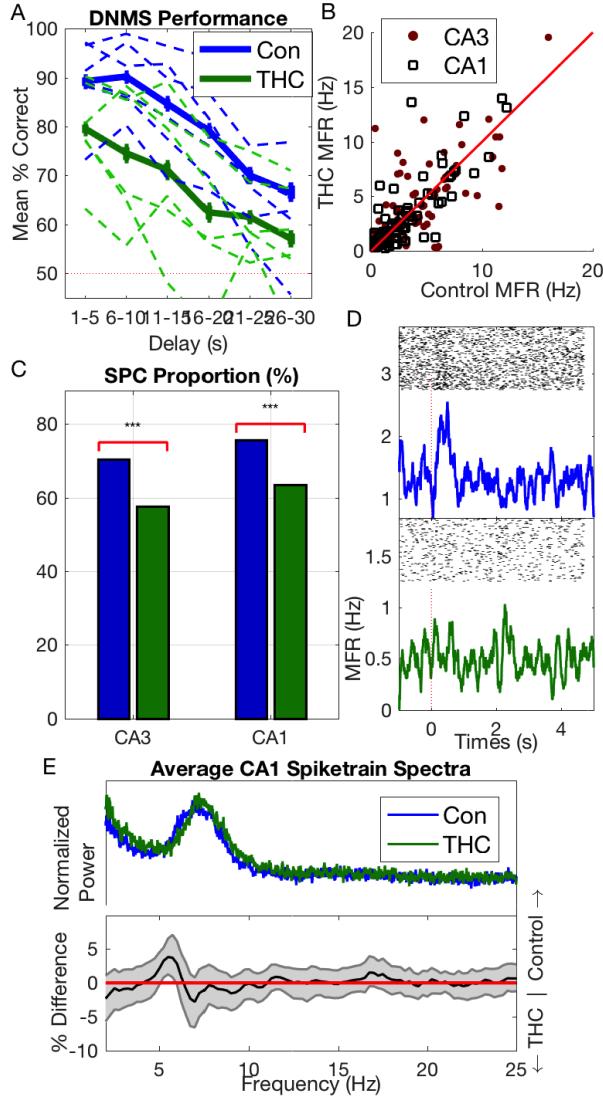
127 (theta oscillations) were only slightly affected. Furthermore behavioral deficits
128 induced by cannabinoids could not be explained by any of these factors, which
129 are the traditional markers of rate and temporal coding in the hippocampus.

130 2.2 Systems Analysis

131 The remainder of the study will focus on systems analysis of the Schaffer col-
132 lateral synapse connecting CA3 to CA1, and how this synapse is affected by
133 THC. Systems analysis aims to identify the input-output "blackbox" by which
134 the input spiketrains are transformed into the output spiketrain. On a more
135 abstract level, it aims to identify how the information encoded in CA3 is prop-
136 agated into CA1. This is distinct from the *signal* analysis done in the previous
137 section which only looks at features of individual spiketrains rather than the
138 causal relationship between multiple spiketrains as done in systems analysis.

139 The relationship between an arbitrary number of input CA3 spiketrains
140 and the output CA1 spiketrain was modeled using a multivariate autoregres-
141 sive model described by Eq. 1 and an example of which is pictured in Fig.
142 2a. Each system consists of N input CA3 neurons and N feedforward filters
143 describing the dynamical input-output relationship between the given CA3 and
144 CA1 neurons (Fig. 2b). Intuitively, these filters can be thought of as the EPSP
145 elicited in the output CA1 neuron in response to an action potential (AP) in
146 the input CA3 neuron. However, unlike EPSPs which traditionally only encap-
147 sulate ion-conductances from neurotransmitter-gated ion channels, the "black-
148 box" nature of the feedforward filters means they also include more complex
149 dynamical effects such as dendritic integration, spike generation, active mem-
150 brane conductances, and feedforward interneuronal inhibition (thereby allowing
151 the filters between two pyramidal cells to be inhibitory). Each model also in-
152 cludes a feedback (autoregressive) filter which describes the effects of past output
153 spikes onto the output present. This filter, which can be intuitively thought of
154 as the afterhyperpotential (AHP) [33] includes intracellular processes such as
155 the absolute and relative refractory periods, slow potassium conductances, and
156 I_h conductances. It also includes more complex intercellular processes such as
157 the recurrent connections between CA1 pyramidal cells and interneurons [34].
158 Neuronal connectivity was estimated using a stepwise input selection procedure.
159 Filter parameters were estimated with Laguerre basis regression using neuronal
160 activity around the sample phase. Model significance was verified using ROC
161 plots and shuffling methods (see supplementary methods).

162 A representative connectivity grid from a recorded THC session with 10
163 recorded neurons (4 CA3, 6 CA1) is shown in Fig. 2a. Fig. 2b shows a sample
164 system from this session between 3 CA3 pyramidal cells and 1 CA1 pyramidal
165 cell. Note that two of the feedforward filters are excitatory (above the x-axis)
166 while the third has both excitatory and inhibitory components, presumably aris-
167 ing through feedforward inhibition involving interneurons [35, 36]. The system
168 also involves a feedback filter which shows a relatively long refractory period
169 ($\sim 40\text{ms}$) followed oscillatory bursting activity. Oscillations in the CA1 pyrami-
170 dal cell AHP are a well known phenomena caused by slow K^+ and I_h conduc-



*Figure 1: (A) Behavioral performance on Delayed-NonMatch-to-Sample (DNMS) task in both control and THC sessions. Dashed lines show individual animal performance, while solid lines show mean performance over all animals. Bars indicate SEM. Dashed red line indicates performance at chance level. (B) Individual neuron mean firing rate (MFR). (C) Sample-presentation cell proportion in CA3 and CA1 cells in control & THC sessions ($^{***}=P < .001$). (D) Example of a sample-presentation cell in a control session (top) which lost its firing specificity under THC (bottom). X-axis shows MFR (Hz) (E) Average CA1 spiketrain spectra (top). Bottom shows mean difference in individual cell spectra (thus it is not simply the difference between the signals in above which are averaged over whole population). Gray error bounds indicate 99% confidence bounds. In (B) and (E), only neurons recorded in at least one control & THC session were included. Results for neurons recorded in several control or THC sessions were averaged over those sessions.*

171 tances, and these oscillations are known to lead to theta resonances [37, 38, 18].
 172 In order to study the filter oscillations more closely, the filter frequency spec-

tra were plotted in Fig. 2c. Both feedforward excitatory filters were found to have peaks in the high theta range (8-9 Hz). Intuitively, this can be understood to mean that information encoded in the theta range in these input neurons is preferentially transmitted to the output CA1 neuron. Furthermore, the feedback filter has a low theta resonance of 3.5 Hz. Significance metrics for the displayed system is shown in Fig. S4, and additional systems are shown in Fig. S5. All together 66% (707/1068) of all systems were found to be significant and 2139 feedforward and 707 feedback filters were obtained. THC was found to reduce the number of significant models per session ($\Delta = -7.4\%$, $P = .011$), but the predictive power of significant models, as measured by AUC (see supplementary methods), was unaltered ($P = .24$).

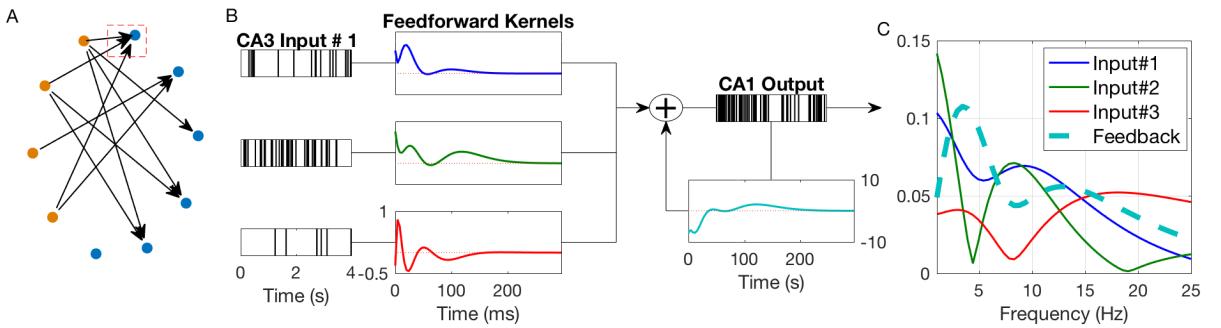


Figure 2: (A) Example connectivity grid of 4 CA3 neurons (orange) and 6 CA1 neurons (blue) recorded during a single session. Note that 1 CA1 neuron has no significant granger-causal inputs. Each line represents a causal connection between those neurons, as encapsulated by a feedforward filter. (B) Example system of CA1 neuron enclosed by the red box in (A). Diagram shows 3 input CA3 spiketrains followed by their respective feedforward filters which are summed with the feedback filter to generate the output CA1 spiketrain. All feedforward filter are plotted with the same y-axis scale. Dashed red line in filter boxes indicates x-axis. (C) Normalized filter spectra computed of feedforward and feedback filters from (B).

To study how THC affects system dynamics on a population level, we examined how features change in the entire sample of control and THC filters. The average filter frequency profile for both control and THC sessions is shown in Fig. 3a,b (top). Both feedforward and feedback spectra are found to have clear theta band peaks, thus generalizing the trend seen in the example system of Fig. 2. This is consistent previous reports which show that CA3 propagates strong theta rhythms to CA1 [39, 40] and also that CA1 is capable to generating endogenous theta rhythms [41]. THC produced a significant decline in the theta power of the feedback filters ($\Delta = 20.8\%$, $P < .001$; Fig. 3b). Note that the feedback filter theta reduction is about 10x stronger than the theta reduction found in the CA1 spiketrain signals (Fig. 1e). No reduction in theta power was found in the feedforward filters ($P = .61$, Fig. 3a). This result suggests that cannabinoid-induced theta desynchronization results primarily from altered feedback properties rather than changes in CA3 \rightarrow CA1 dynamics.

Cannabinoids have been reported to affect network excitation-inhibition bal-

199 ance (EIB) [10, 42]. Particularly, there is much debate whether cannabinoids are
 200 pro- or anticonvulsants [8, 43, 44, 4, 6]. In order to examine the effects cannabinoids
 201 have on network EIB, we quantified the excitation of the estimated filters
 202 using a metric called the excitatory index (EI), which is the ratio between pos-
 203 itive filter area and total filter area. It was found that THC had no significant
 204 effect on feedforward EI ($P = .14$); however, there was an insignificant trend
 205 showing that THC-induced decreases in feedforward EI were correlated with be-
 206 havioral deficits ($R^2 = .27, P = .063$, Fig. 3c). Additionally, THC reduced the
 207 number of casually connected CA3-CA1 neuronal pairs ($\Delta = -8.9\%, P < .001$).
 208 These findings, together with the THC-induced decrease of CA3→CA1 signifi-
 209 cant models, suggest that THC reduces the causal influence CA3 neurons have
 210 on CA1 spiketimes. In other words, THC can be said to functionally isolate
 211 CA1 from CA3. It was also found that THC significantly increased feedback EI
 212 ($\Delta = 3.5\%, P = .022$) and that the increased feedback EI was correlated with
 213 behavioral deficits ($R^2 = .38, P = .007$, Fig. 3d).

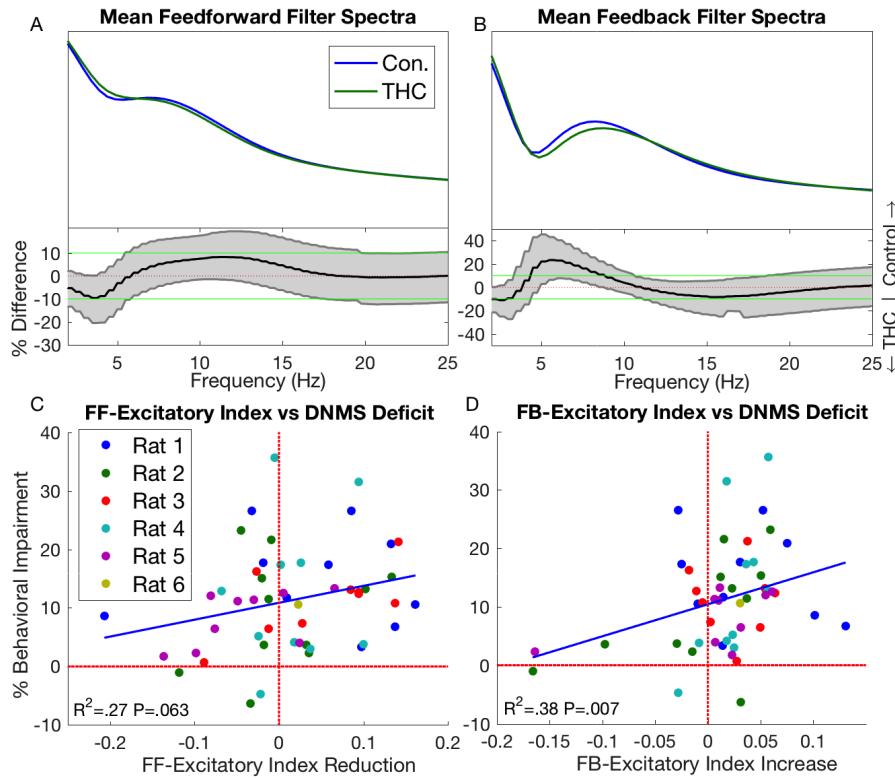


Figure 3: Average feedforward (A) and feedback (B) filter spectra in control and THC sessions (top), and their differences (bottom). Same format and analysis as Fig. 1a. (C) Correlation between feedforward filter excitatory index (EI) reduction and behavioral deficits. Each point represents a specific THC session, with points of the same color coming from the same animal. X-axis shows reduction in feedforward EI, while y-axis shows reduction in behavioral performance. Both reductions were taken relative to control sessions (see supplemental methods). (D) Same as (C) but for feedback EI increase.

214 **2.3 PDM Analysis**

215 The large quantity (>2800) and variability of the obtained filters describing
216 the CA3 \rightarrow CA1 dynamic transformation presents a challenge of interpretation.
217 Namely, how could one identify features from the entire filter population which
218 are representative of the CA3 \rightarrow CA1 transformation rather than just the input-
219 output relationship found in this or that particular pair of neurons. In essence
220 this is an unsupervised learning problem which aims to identify hidden structure
221 within the filter population for the purpose of knowledge discovery. Our group
222 has developed the concept of the global principal dynamic modes (gPDMs) to-
223 wards this effort [19, 45, 46]. The gPDMs are a system-specific and efficient basis
224 set which contain the essential dynamic components of the filter population and
225 are meant to be amenable to biological interpretation. One set of gPDMs were
226 estimated from all (control and THC) obtained filters with the hypothesis that
227 THC would primarily change the expression strength of the gPDMs rather than
228 their specific shapes.

229 Fig. 4a,b shows the obtained feedforward and feedback gPDMs in both the
230 time and frequency domain. Once again, the feedforward and feedback gPDMs
231 represent the dominant independent components of feedforward and feedback
232 kernels, respectively. The first feedforward gPDM was found to have almost all
233 its energy in the 1st time bin, with an immediate decline thereafter. This gPDM
234 represents near concurrent firing between CA3 and CA1 neurons and presum-
235 ably results from both direct CA3 \rightarrow CA1 connections via the Schaffer collateral
236 synapse [47, 48] and common inputs from the entorhinal cortex [49, 50]. The
237 third feedforward gPDM, which is characterized by an initial inhibitory phase,
238 presumably represents feedforward interneuronal inhibition which is prevalent in
239 the CA3 \rightarrow CA1 connection [35, 36]. THC was not found to influence the strength
240 of either of these gPDMs ($P = .76$, $P = .60$; Fig. S6). The second feedforward
241 gPDM which is characterized by sustained and oscillatory excitation was found
242 to have a strong theta peak in the frequency domain. Furthermore, it was found
243 that THC-induced declines in the strength of this gPDM were correlated with
244 behavioral deficits ($R^2 = .30$, $P = .032$; Fig. 4c).

245 The three obtained feedback gPDMs are shown in Fig. 4b. These gPDMs
246 express the essential feedback dynamics found in CA1 neurons. As previously
247 mentioned, these dynamics arise through the combination of intracellular pro-
248 cesses such as the AHP and extracellular processes such as recurrent connections
249 between CA1 pyramidal cells and interneurons. It was found that THC-induced
250 increases in the third feedback gPDM were correlated with behavioral deficits
251 ($R^2 = .39$, $P = .005$; Fig. 4d). This correlation was not seen in either of the first
252 two feedback gPDMs ($P = .32$, $P = .75$; Fig. S6). Notably, the 3rd feedback
253 gPDM was seen to be "theta-blocking" in the frequency domain due to its trough
254 at 8 Hz. This gPDM counteracts the 1st "theta-promoting" feedback gPDM and
255 disrupts theta oscillations in the CA1 neuron. The THC-induced changes in the
256 feedforward and feedback theta gPDMs paint a more complete picture of the
257 CA1 theta reductions seen in Fig. 1e. Namely, they attribute the theta losses
258 to specific feedforward and feedback dynamical filters which may potentially be

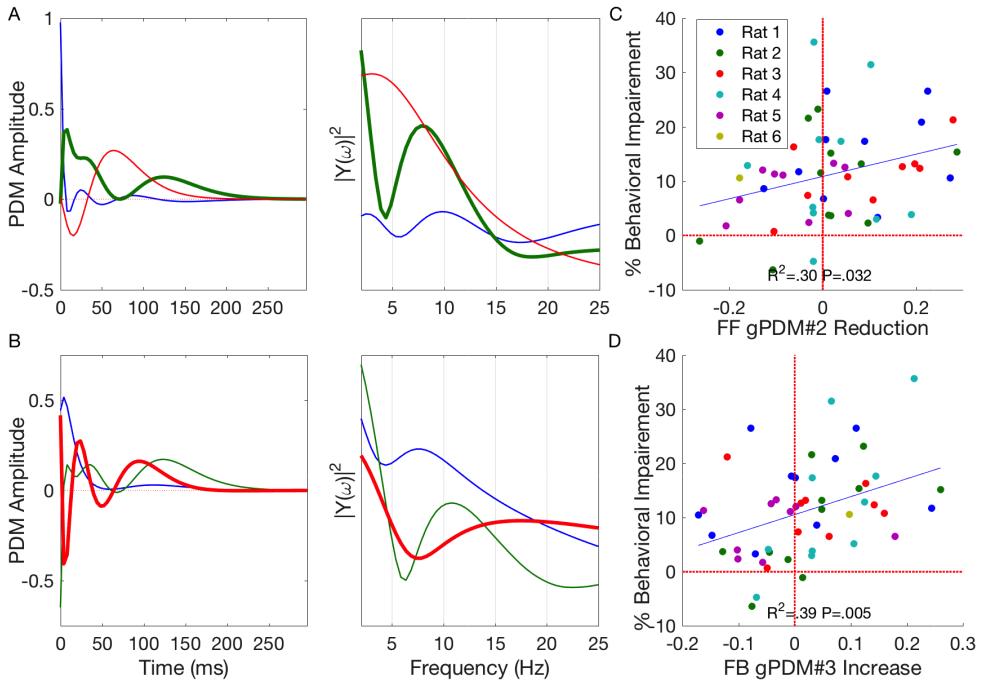


Figure 4: Feedforward (A) and feedback (B) global principal dynamic modes (gPDMs) in both the time (left) and frequency domain (right). Reductions in 2nd feedforward gPDM (C) and increases in 3rd feedback gPDM (D) were found to be correlated with behavioral deficits. Same format as Fig. 3.

traced to specific biophysical mechanisms. Furthermore, changes in these dynamical filters have been specifically correlated with behavioral deficits, which could not be done with theta reductions in the CA1 signal (Fig. S3).

3 Discussion

The current study uses 'data-driven' nonparametric system dynamics modeling tools to study the effects of THC on the Schaffer Collateral synapse in rodents. The chief findings of the study can be summarized as: (1) THC induced little or no change in traditional rate and temporal coding metrics such as MFR and theta power, (2) THC altered the CA1 excitatory-inhibitory balance by reducing feedforward influence from CA3 while increasing feedback excitation from CA1, (3) THC reduced theta information flow through the Schaffer collateral synapse, and (4) The magnitudes of both of the previous effects were directly correlated with the severity of behavioral deficits induced by THC. Overall these results suggest the conclusion that THC impairs memory encoding by functionally isolating CA1 from CA3.

From a computational perspective, the nonparametric modeling methods used in this study proved successful in studying the network level effects of cannabinoids since, unlike biophysical models, all model parameters were estimated directly from recorded data and very few *a priori* assumptions were

made about the effects of THC [19, 20, 51]. The global principal dynamic modes (gPDMs), which were derived from MVAR filters of the entire population of neurons, further extracted hidden dynamical structure from 'noisy' neuron-neuron variability. Importantly, THC-induced changes in the gPDMs were directly correlated with behavioral impairments, thus justifying their utility. Furthermore, while most in-vivo studies on THC analyze macro level signals such as ECoG and EEG, this work adds to a relatively small body of literature which analyzes the effects of THC on neuronal population spiking activity. Finally, to our knowledge, this is the first work which examines the effect of THC on neuronal systems dynamics, or the causal interactions between signals, rather than on neuronal signals themselves.

It was found that THC increased feedback excitatory index in CA1 and that the magnitude of this effect was correlated with behavioral deficits. We hypothesize that this is due to reduced feedback inhibition from CA1 cholecystokinin (CCK)-containing cells. While CCK cells only make up only 13.9% of interneurons [52], they express significantly more CB1 receptors than any other cell in the hippocampus [53], and their primary output is to CA1 pyramidal cells [52]. Increased THC concentrations would reduce CCK interneuron output by (1) reducing the amount of GABA they release per action potential (2) reducing their MFR due to reduced glutamatergic input from principal cells in both CA3 and CA1 [54, 55].

It was also found that THC reduced the number of casually connected CA3-CA1 neuronal pairs; furthermore there was an interesting but insignificant trend for THC-induced deficits in feedforward excitation to lead to behavioral deficits. This trend may prove to be significant given a higher sample size. We hypothesize that this reduced feedforward influence is caused by decreased glutamate release from CA3 pyramidal cells due to CB1 receptor activation by THC [56]. Even though pyramidal cells have much lower densities of CB1 receptors than interneurons [53, 57], there is evidence that CB induced reduction of excitation is larger than these relative densities suggest. Principal cells outnumber interneurons 20:1 in CA1 [50] and their CB1 receptors were found to be several fold more efficacious than those of interneurons [58]. Further, lower baseline activation levels of CB1 receptors on principal cells than on interneurons suggest they would be disproportionately activated by CB agonists [59]. Altogether, the decreased feedback inhibition and feedforward excitation amount to a functional isolation, or breakdown in information flow between CA3 and CA1. We suggest that this functional isolation is responsible for the behavioral impairments seen in the DNMS task.

The 'functional isolation' hypothesis is further supported by previous work which showed that the behavioral impairments caused by cannabinoids in the DNMS task were similar to those seen with a full pharmacological lesion of the hippocampus [60]. Given the centrality of CA3→CA1 information flow to hippocampal function, a functional isolation of these areas could indeed presumably lead to impairments similar to that of a full lesion. Relatedly, Goonawardena et al. [25] injected THC intraperitoneally at low 1 mg/kg doses as in this study and in higher doses of 3 mg/kg. They found that while both doses disrupted

324 hippocampal synchrony, only the higher dose resulted in a reduction in pyramidal cell MFR. This suggests that at the lower dose both previously described
325 phenomena are at a net balance, while at the higher dose, the decrease in feed-
326 forward excitation overpowers the increase in feedback excitation and results in
327 lower MFR. Finally, the hypothesis predicts a breakdown in the normal spike-
328 time coordination between pyramidal cells and interneurons in CA1 circuits.
329 The breakdown of this coordination, which has been extensively implicated in
330 hippocampal oscillations [61, 62], could be responsible for the observed decrease
331 in theta oscillations and information flow.

332 Although the current results only suggest this hypothesis, several experi-
333 ments could be done to further substantiate it. Feedforward and feedback ker-
334 nels and gPDMs could be estimated at different doses of THC; the hypothesis
335 would predict that different doses would effect the two processes independently,
336 with one of the two processes potentially being more dominant at different THC
337 levels. Significant developments in in-vivo synaptic patch clamping [63] and cal-
338 cium imaging in recent years could be used to directly measure the drive of CCK
339 cells and CA3 pyramidal cells onto CA1 pyramidal cells under THC.

340 Much research has been done investigating the effects THC and other canna-
341 noids have on seizures and epilepsy. Results so far have been mixed, with various
342 studies showing that THC is both pro- and anticonvulsant [3, 4, 5, 6, 7, 8, 7].
343 The results from this study and the presented hypothesis suggest that THC in-
344 herently is not pro- or anti-convulsant but that its effects will depend on the
345 dosage and the unique circuitry of every epileptic focus. Interestingly, a study
346 by Rudenko et al. [6] has shown that indeed the effects of a CB1 agonist were
347 dose dependant, with *lower* doses being anticonvulsant and higher doses being
348 proconvulsant. Finally, this study suggests that in order to truly understand the
349 effects of THC on epileptic circuits, one must study the systems level changes
350 in circuit dynamics rather than taking a reductionist approach and studying the
351 effects of THC on any particular receptor or cell type.

352 The present study analyzed the effects of THC from both a signals and sys-
353 tems perspective - and found that systems analysis yielded much richer results.
354 For example, while analysis of CA1 spiketrain signals showed a slight (2%) re-
355 duction in theta frequency, analysis of system kernels showed that the theta loss
356 was primarily due to CA1 feedback dynamics whose kernels lost over 20% of their
357 theta power, while theta power in feedforward kernels was unaffected. Further-
358 more, only systems analysis allows one to analyze predictive power, feedforward
359 and feedback excitation, and EPSP and AHP waveform shape. Notably, the
360 finding that feedforward influence decreased while feedback excitation increased
361 could not have been observed using only signal analysis which would have only
362 detected a constant MFR.

363 The present study also employed gPDMs as a means to extract the most
364 significant information from the kernel dynamics estimated from several animals
365 over several sessions [19, 64, 18, 48]. The utility of the gPDM method was justi-
366 fied by the finding that reductions in theta related gPDMs in a given session were
367 directly correlated with behavioral deficits, showing that the gPDMs can isolate
368 the particular dynamics which are most affected by THC. Furthermore, THC-

370 induced theta power losses in spiketrain signals were not found to be correlated
371 with behavioral deficits. Although in the present study, kernels and gPDMs were
372 restricted to being linear in order to more easily quantify their overall strength
373 and excitation (via the EI), future work will aim to identify the effects of THC
374 on hippocampal nonlinear dynamics [65, 51].

375 **Ethics Statement**

376 All animal protocols were approved by the Wake Forest University Institutional
377 Animal Care and Use Committee, in accordance with the Association for Assess-
378 ment and Accreditation of Laboratory Animal Care and the National Institute
379 of Health Guide for the Care and Use of Laboratory Animals (NIH Publication
380 No. 8023).

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383 Biomedical Simulations Resource at the University of Southern California.

384 **4 Methods**

385 **4.1 Experimental Procedures**

386 N=6 Male Long-Evans rats were trained to criterion on a two lever, spatial
387 Delayed NonMatch-to-Sample (DNMS) task (see Fig. S1). Briefly, during the
388 sample phase the rat was presented one of two levers (left or right). After a delay
389 phase ranging from 1-30 seconds, the rat was presented both levers and had to
390 choose the opposite lever in order to attain a reward. After training, two identical
391 electrode arrays (Neurolinec, New York, NY), each consisting of two rows of eight
392 stainless steel wires (diameter: 20 μm) were implanted bilaterally over the dorsal
393 hippocampus (see Fetterhoff et al. [21] for more details). The array was designed
394 such that the distance between two adjacent electrodes within a row was 200 μm
395 and between rows was 400 μm to conform to the locations of the respective CA3
396 and CA1 cell layers.

397 Each rodent underwent 16-25 sessions of the task, which were roughly evenly
398 divided between control and THC sessions, wherein the rodent was intraperi-
399 toneally administered 1 mg/kg of body weight Δ^9 -tetrahydrocannabinol (THC),
400 an exogenous cannabinoid found in marijuana. During the task, spike trains
401 were recorded in-vivo with multi-electrode arrays implanted in the left and right
402 CA3 and CA1 regions of the hippocampus. In an effort to acquire a consistent
403 cognitive state, only spiking activity around the sample phase of the task was
404 used. Spikes from multiple trials were sorted, time-stamped, and concatenated
405 into a discretized binary time series using a 4ms bin. For more details on the
406 experimental setup, see supplementary methods.

407 4.2 Model Configuration and Estimation

408 Nonparametric multiple-input linear autoregressive models were used to model
 409 the dynamical transformation between input and output spike trains (see Fig.
 410 2,5) [18, 51]. Each model consisted of a feedforward component, reflecting the
 411 effect of the N input cells on the output cell and a feedback (autoregressive)
 412 component reflecting the subthreshold and suprathreshold effects the output
 413 cell has on itself. Thus, the output $y(t)$ is calculated as:

$$y(t) = \sum_{n=1}^N \sum_{\tau=0}^M k_n(\tau) x_n(t-\tau) + \sum_{\tau=1}^{M+1} k_{AR}(\tau) y(t-\tau) \quad (1)$$

414 where k_n reflects the feedforward filter of input $x_n(t)$, and k_{AR} reflects the feed-
 415 back filter. In order to reduce the number of model parameters and thereby
 416 increase parameter stability, we applied the Laguerre expansion technique to ex-
 417 pand the feedforward and feedback filters over L Laguerre basis functions (see
 418 supplementary methods).

419 Effective connectivity between neurons was assessed using a Granger causality-
 420 like approach. For each output CA1 neuron, input CA3 neurons were selected
 421 in a forward stepwise procedure whereby only neurons which help predict the
 422 output CA1 spike activity were included in the model. After all input neurons
 423 were selected, a Monte Carlo approach was used to assess model significance. A
 424 model was deemed significant if the CA3 inputs could predict the output CA1
 425 activity significantly better ($P < .0001$) than randomly permuted versions of the
 426 inputs. See supplementary methods for more details.

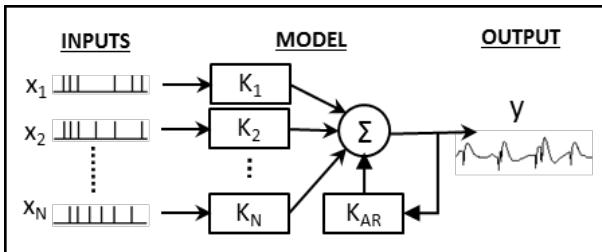


Figure 5: Model Configuration. Each model has N point-process inputs which each go through a linear filter, K_i . These inputs are then summed with the output of the feedback filter, K_{AR} to generate the final output, $y(t)$, which is a continuous signal

427 4.3 Principal Dynamic Modes

428 The global principal dynamic modes (gPDMs) were obtained in a two step pro-
 429 cess: first, all filters of each input from every animal were concatenated in a
 430 rectangular matrix. Then singular value decomposition (SVD) was performed
 431 on the rectangular matrix to obtain all the significant singular vectors, which
 432 are the gPDMs. It was found that 3 gPDMs were sufficient to describe the lin-
 433 ear dynamics both the population of feedforward and feedback filters. gPDM
 434 strength in a given filter was computed by taking the dot product between the

435 gPDM and the filter. gPDM strength in a given session was computed by taking
436 the average gPDM strength in every filter of that session.

437 **A Supplementary Methods**

438 All data was previously used in a study on the effects of cannabinoids on hip-
439 pocampal multifractality [21, 22])

440 **A.1 Animals**

441 Subjects were Long-Evans rats (Harlan) aged 4–6 months ($n = 6$) individually
442 housed and allowed free access to food with water regulation to maintain 85% of
443 ad libitum body weight during testing. All animal protocols were approved by
444 the Wake Forest University Institutional Animal Care and Use Committee, in
445 accordance with the Association for Assessment and Accreditation of Laboratory
446 Animal Care and the National Institute of Health Guide for the Care and Use
447 of Laboratory Animals (NIH Publication No. 8023).

448 **A.2 Apparatus**

449 The behavioral testing apparatus for the delayed nonmatch-to-sample (DNMS)
450 task is the same as reported in other studies [23] and consisted of a 43x43x50 cm
451 Plexiglas chamber with two retractable levers (left and right) positioned on either
452 side of a water trough on the front panel. A nosepoke device (photocell) was
453 mounted in the center of the wall opposite the levers with a cue light positioned
454 immediately above the nosepoke device. A video camera was mounted on the
455 ceiling and the entire chamber was housed inside a commercially built sound-
456 attenuated cubicle.

457 **A.3 DNMS Task**

458 The DNMS task consisted of three main phases: Sample, Delay and Nonmatch.
459 The sample phase initiated the trial when either the left or right lever was
460 extended (50% probability), requiring the animal to press it as the Sample Re-
461 sponse (SR). The lever was then retracted and the Delay phase of the task
462 initiated, as signaled by the illumination of a cue light over the nosepoke pho-
463 tocell device on the wall on the opposite side of the chamber. At least one
464 nosepoke (NP) was required following the delay interval which varied randomly
465 in duration (1-30 s) on each trial during the session. The Nonmatch phase began
466 when the delay timed out, the photocell cue light turned off and both the left
467 and right levers on the front panel were extended. Correct responses consisted
468 of pressing the lever in the Nonmatch phase located in the spatial position op-
469 posite the SR (nonmatch response: NR). This produced a drop of water (0.4
470 ml) reward in the trough between the two levers. After the NR the levers were
471 retracted for a 10.0 second intertrial interval (ITI) before the next Sample lever
472 was presented to begin the next trial. A lever press at the same position as the
473 SR (match response) constituted an “error” with no water delivery and turned

474 off of the chamber house lights for 5.0s and the next trial was presented 5.0 s
475 later. Individual performance was assessed as % NRs (correct responses) with
476 respect to the total number of trials (80-100) per daily (1 hr) sessions.

477 A.4 Drug Preparation & Administration

478 Δ^9 -tetrahydrocannabinol (THC) was obtained from the National Institute on
479 Drug Abuse as a 50 mg/ml solution in ethanol. Detergent vehicle was pre-
480 pared from Pluronic F68 (Sigma, St. Louis, MO), 20 mg/ml in ethanol. THC
481 was added to the detergent-ethanol solution (0.5 ml of either THC), and then 2.0
482 ml of saline (0.9%) was slowly added to the ethanol-drug solution. The solution
483 was stirred rapidly and placed under a steady stream of nitrogen gas to evapo-
484 rate the ethanol (~10 min). This resulted in a detergent-drug suspension (12.5
485 mg/ml THC), which was sonicated and then diluted with saline to final injec-
486 tion concentrations (0.5-2.0 mg/ml THC). On drug administration days, animals
487 were injected intraperitoneally with the drug-detergent solution (1 mg/kg) ~10
488 min before the start of the behavioral session. Our experience with these ex-
489 periments has shown that performance after vehicle injection is not significantly
490 different than no injection, and therefore was omitted during this series of ex-
491 periments to minimize risk of infection to the animals. At least two no injection
492 days were imposed between each drug-testing session. All drug solutions were
493 mixed fresh each day.

494 A.5 Surgery

495 All surgical procedures conformed to National Institutes of Health and Associa-
496 tion for Assessment and Accreditation of Laboratory Animal Care guidelines,
497 and were performed in a rodent surgical facility approved by the Wake Forest
498 University Institutional Animal Care and Use Committee. After being trained to
499 criterion performance level in the DNMS task animals were anesthetized with ke-
500 tamine (100 mg/kg) and xylazine (10 mg/kg) and placed in a stereotaxic frame.
501 Craniotomies (5mm-diameter) were performed bilaterally over the dorsal hip-
502 pocampus to provide for implantation of 2 identical array electrodes (Neurolinc,
503 New York, NY), each consisting of two rows of 8 stainless steel wires (diameter:
504 20 μ m) positioned such that the geometric center of each electrode array was
505 centered at co-ordinates 3.4 mm posterior to Bregma and 3.0 mm lateral (right
506 or left) to midline [66]. The array was designed such that the distance between
507 two adjacent electrodes within a row was 200 μ m and between rows was 400
508 μ m to conform to the locations of the respective CA3 and CA1 cell layers. The
509 longitudinal axis of the array of electrodes was angled 30° to the midline during
510 implantation to conform to the orientation of the longitudinal axis of the hip-
511 pocampus, with posterior electrode sites more lateral than anterior sites. The
512 electrode array was lowered in 25-100 μ m steps to a depth of 3.0 - 4.0 mm from
513 the cortical surface for the longer electrodes positioned in the CA3 cell layer,
514 leaving the shorter CA1 electrodes 1.2 mm higher with tips in the CA1 layer.
515 Extracellular neuronal spike activity was monitored from all electrodes during
516 surgery to maximize placement in the appropriate hippocampal cell layers. After

517 placement of the array the cranium was sealed with bone wax and dental cement
518 and the animals treated with buprenorphine (0.01–0.05 mg/kg) for pain relief
519 over the next 4-6 hrs. The scalp wound was treated periodically with Neosporin
520 antibiotic and systemic injections of penicillin G (300,000 U, intramuscular) were
521 given to prevent infection. Animals were allowed to recover from surgery for at
522 least 1 week before continuing behavioral testing [67].

523 **A.6 Electrophysiological Monitoring & Preprocessing**

524 Animals were connected by cable to the recording apparatus via a 32-channel
525 headstage and harness attached to a 40-channel slip-ring commutator (Crist
526 Instruments, Hagerstown, MD) to allow free movement in the behavioral test-
527 ing chamber. Single neuron action potentials (spikes) were isolated by time-
528 amplitude window discrimination and computer-identified individual waveform
529 characteristics using a multi-neuron acquisition (MAP) processor (Plexon Inc.,
530 Dallas, TX, USA). Single neuron spikes were recorded daily and identified us-
531 ing waveform and firing characteristics within the task (perievent histograms)
532 for each of the DNMS events (SR, LNP & NR). To maintain waveform shape
533 across days, all recorded data was concatenated into one file (separately for each
534 rat) and offline sorting was performed using principal component analysis, peak-
535 valley, and nonlinear energy algorithms in Offline Sorter (Plexon Inc., Dallas,
536 TX, USA). Hippocampal neuron ensembles used to distinguish recording phases
537 and drug treatment conditions consisted of 10-30 single neurons, each recorded
538 from a separate identified electrode location on either of the bilateral arrays.
539 All isolated spike trains contained no less than a 1 ms gap at the center of the
540 autocorrelogram. No effort was made to differentiate between principal cells and
541 interneurons. Previous work has shown that hippocampal neurons recorded with
542 the same waveform from the same electrodes exhibit consistent mean, baseline
543 and DNMS task modulated firing rate alterations [68, 26], and therefore indi-
544 vidual neurons were treated as the same when recorded over multiple days. A
545 total of 189 neurons recorded during 5,143 recording phases were analyzed in
546 the reported experiments.

547 **A.7 Sample-Response Cell Identification**

548 Prior studies from this laboratory have identified hippocampal neurons recorded
549 as above by “Functional Cell Types” (FCTs) described by different behavioral
550 correlates of DNMS task-related events such as lever position and/or phase of
551 the task [26, 25]. Sample-response cells, a subtype of FCTs, were identified by
552 first constructing a smoothed (51 bin) perievent histogram around the sample
553 presentation phase of the DNMS task. The neurons background firing rate mean
554 and variance were calculated from activity 3.5-5s after sample presentation. If
555 the neuron’s MFR from the 2 second window around sample presentation was
556 4 standard deviations greater than its MFR from the background period it was
557 classified as a sample-response cell. It should be noted that for the purpose of
558 this paper other FCTs such as those which respond to a specific lever (left/right)
559 or trial-type cells were not considered [69].

560 **A.8 Laguerre Expansion Technique**

561 In order to apply the Laguerre expansion technique [19], the input and output
 562 data records were first convolved with the Laguerre functions:

$$v_{x_i}^{(l)} = \sum_{\tau=0}^M b_l(\tau) x_i(t - \tau) \quad (2)$$

563

$$v_y^{(l)} = \sum_{\tau=0}^M b_l(\tau) y(t - \tau) \quad (3)$$

564 where b_l is the l^{th} Laguerre basis function. By first convolving with the Laguerre
 565 basis functions, the dynamical effects of the past input epochs are removed and
 566 we are left with a simple regression of contemporaneous data. Substituting the
 567 above equations into equation 1, we have:

$$y(t) = k_0 + \sum_{n=1}^N \sum_{l=1}^L c_{l,x_i}(l) v_{l,x_i}(t) + \sum_{l=1}^L c_{l,y}(l) v_{l,y}(t) \quad (4)$$

568 where c_{l,x_i} and $c_{l,y}$ are the feedforward and feedback Laguerre expansion coeffi-
 569 cients. To estimate model parameters, eq. 4 was cast in matrix form:

$$\mathbf{y} = \mathbf{V}\mathbf{c} + \epsilon \quad (5)$$

570 where \mathbf{y} is the vector of all N output samples, \mathbf{V} is the design matrix consisting
 571 of the convolved inputs, \mathbf{c} are the model parameters to be estimated, and ϵ is
 572 the modeling error. Eq. 5 was solved using least squares regression (LSR). The
 573 memory of our system was fixed at 300ms, in accordance with previous studies
 574 [65, 70]. The Laguerre parameter α was fixed at 0.6 to reflect this system memory
 575 [19].

576 **A.9 Model Selection**

577 In theory, the most predictive model would include all recorded inputs. However,
 578 such a model would be susceptible to overfitting, and would not reveal which
 579 neurons are causally connected to each other. To overcome this issue a forward
 580 step-wise selection procedure was used to minimize overfitting and prune out
 581 all inputs which are not causally related to the output [71]. Given an output
 582 cell and M potential input cells recorded during the same session, the following
 583 steps were used to select the N input cells which are causally connected to the
 584 output cell. First, the data was divided into training (in-sample) and testing
 585 (out-of-sample) sets. Then, M single-input single-output (SISO) models were
 586 constructed with each of the potential inputs. The model whose predicted output
 587 had the highest correlation, as measured by the Pearson correlation-coefficient,
 588 ρ , with the actual output was selected. Afterwards, $N-1$ models were constructed
 589 with two inputs: the previously selected input and one of the remaining potential
 590 inputs. If any of the inputs were able to raise ρ , the input which raised ρ the

591 most was selected; otherwise, the procedure was ended, and only 1 input was
592 selected. This procedure was repeated until either none of the inputs were able
593 to raise ρ , or all M potential neurons were selected. The N selected neurons
594 were then used as the model input.

595 A.10 Model Validation

596 To avoid overfitting, Monte Carlo style simulations were used to select those
597 models which represent significant causal connections between input and output
598 neurons and do not just fit noise [72]. The following procedure was used: in
599 each run the real input was randomly permuted with respect to the output. A
600 model was then generated between the permuted input and the real output, and
601 the Pearson correlation coefficient, ρ_i , was obtained as a metric of performance.
602 T=40 such simulations were conducted for each output and a set of performance
603 metrics, $\{\rho_i\}_i^T$, was obtained. Then, using Fisher's transformation, we tested the
604 hypothesis, H_0 , that ρ was within the population of $\{\rho_i\}$. If this hypothesis could
605 be rejected at the 99.99% significance level, the model was deemed significant.
606 The very conservative threshold ($P < .0001$) was used due to the large number
607 of comparisons being made.

608 A.11 Statistical Analysis

609 Unless otherwise noted, the unpaired Mann-Whitney U test was used to access
610 whether significant differences exist between two samples. This test was used
611 since it does not assume a normal distribution, and much of our data was found to
612 be skewed/nonnormal. Shift estimates (Hodges-Lehman) and confidence inter-
613 vals were estimated as prescribed by Higgins [73]. In order to estimate the scale
614 estimate, or the ratio between two samples, the data was first log-transformed
615 and then scale estimate was taken to be the antilog of the shift estimate. The
616 χ^2 test was used to compare proportions.

617 In addition to the Pearson correlation coefficient, ρ , Receiver Operating Char-
618 acteristic (ROC) curves were used to visualize model performance. ROC curves
619 plot the true positive rate against the false positive rate over the putative range
620 of threshold values for the continuous output, y [72]. The area under the curve
621 (AUC) of ROC plots are used as a performance metric of the model, and have
622 been shown to be equivalent to the Mann-Whitney two sample statistic [74].
623 The AUC ranges from 0 to 1, with 0.5 indicating a random predictor and higher
624 values indicating better model performance. The ρ and AUC metrics were cho-
625 sen as they measure the similarity between a continuous 'prethreshold' signal
626 and a spike train. The continuous 'prethreshold' signal was chosen over adding
627 a threshold trigger and comparing true output spike train with an output 'post-
628 threshold' spike train for two reasons. First, this allows us to avoid specifying the
629 threshold trigger value, which relies on the somewhat arbitrary tradeoff between
630 true-positive and false-negative spikes [45]. Also, similarity metrics between two
631 spike trains often require the specification of a 'binning parameter' to determine

the temporal resolution of the metric [75, 76].¹

633 B Supplementary Figures

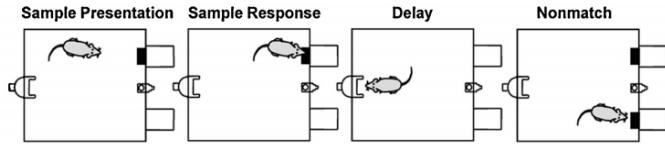


Figure S1: Schematic of the DNMS task. First the rat is presented with one of two levers (sample presentation), which it presses (sample response). Then following a delay phase, the rat is presented with both levers (Nonmatch), of which it must press the opposite lever from which it was presented in order to successfully complete the task.

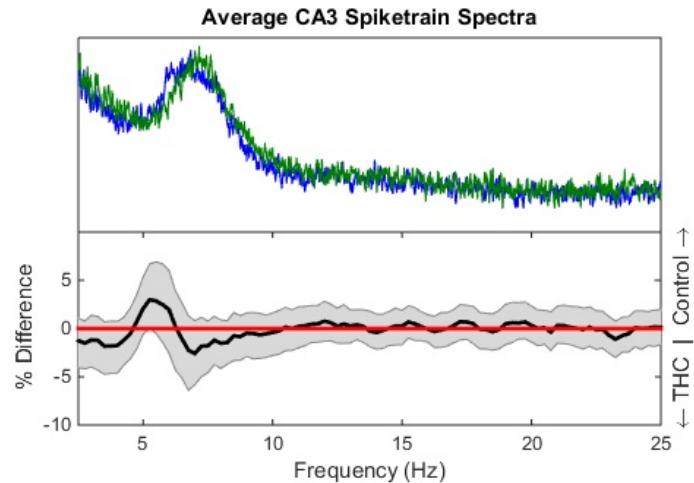


Figure S2: CA3 spectra mean frequency and differences. Same format as Fig. 1e. A weak but significant trend was found for declining CA3 theta oscillations ($\Delta = 1.94\%$, $P = .045$).

¹I should probably add sections on how behavioral correlation analysis & FFT was done...

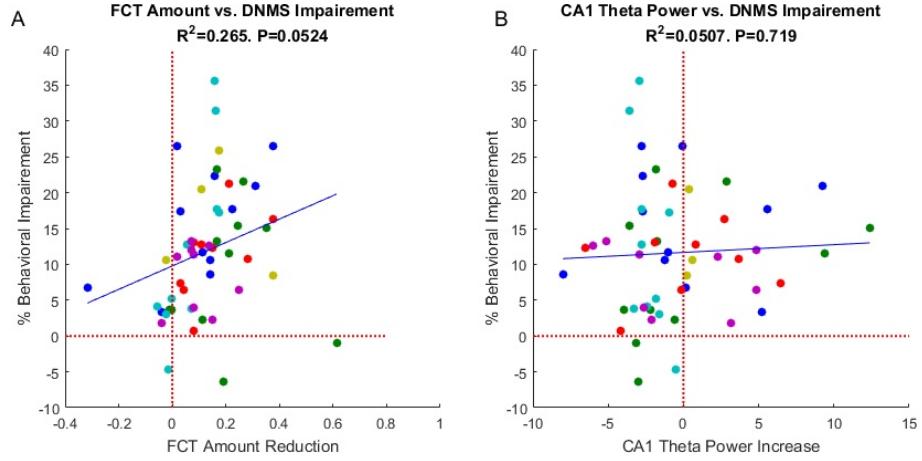


Figure S3: (A) A suggestive but insignificant relationship was found between the THC-induced decrease in the mean number of sample-presentation cells and behavioral performance ($R^2 = .265$, $P = .052$). (B) No relationship was found between reductions in CA1 theta power and behavioral impairment ($P = .67$). Format is same as Fig. 3.

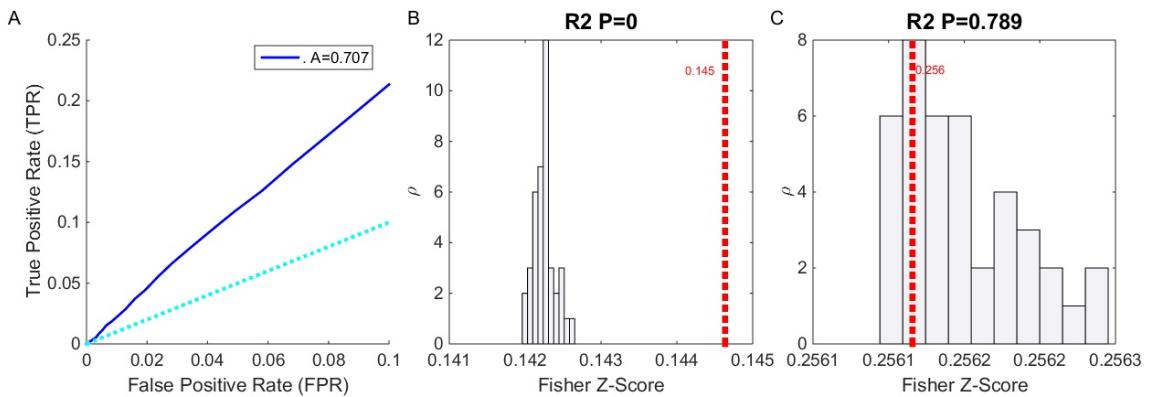


Figure S4: (A) ROC plot (see supplementary methods) for model shown in Fig. 2 showing model predictive power. The light blue line ($TPR=FPR$) indicates a model with no predictive power. (B,C) Examples of Monte Carlo simulations: For each model, 40 surrogate models with shuffled inputs were generated. The Fisher z-scores of these models, which are derived from ρ , were plotted as a histogram, while the true ρ value is the plotted dashed red line. The P value for the hypothesis that the true ρ value is greater than the simulated ρ values is printed above the graphs. Models were deemed significant if $P < .0001$. (B) shows the results for the model in Fig. 2, which was deemed significant. (C) shows an insignificant model

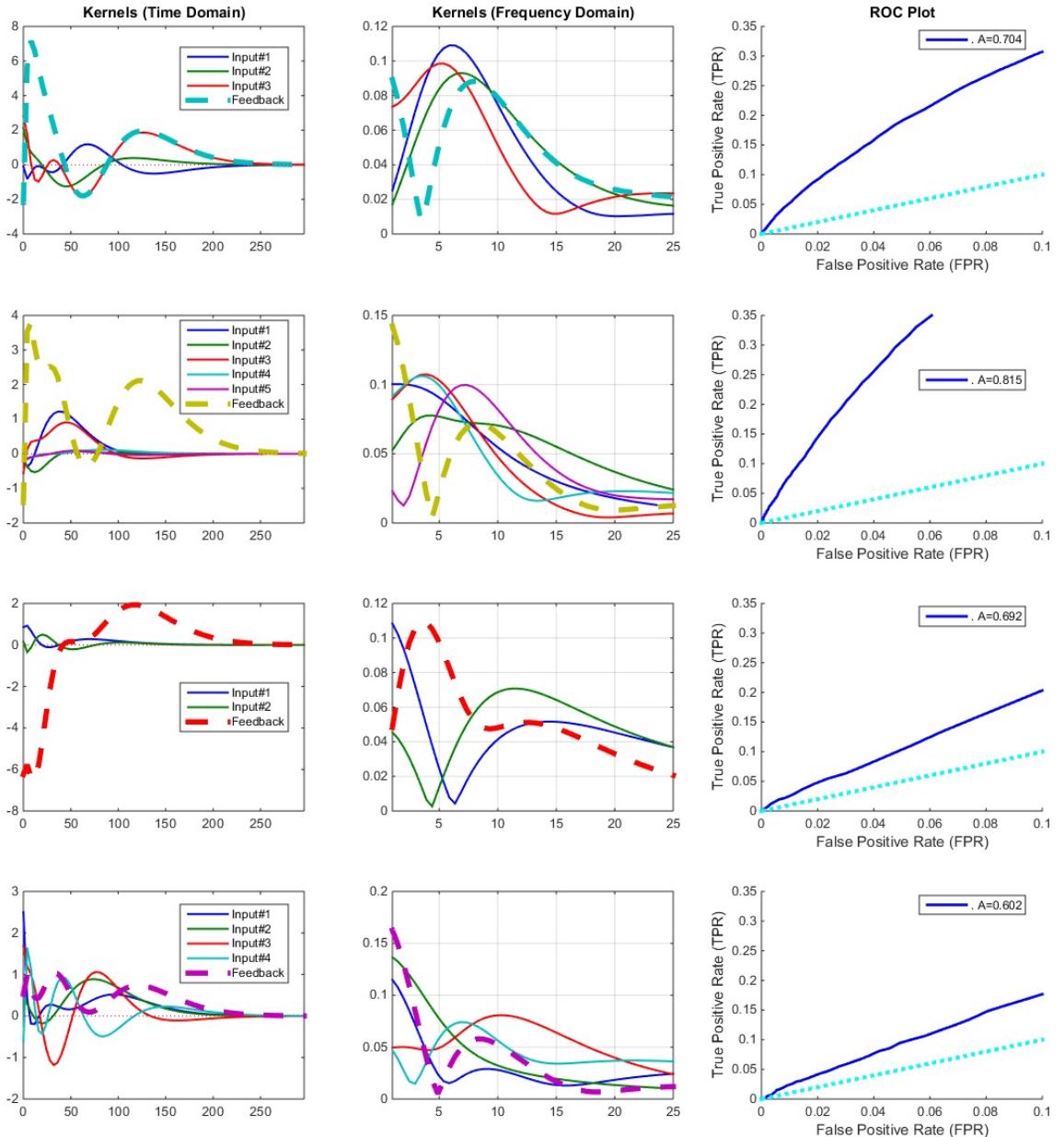


Figure S5: 4 additional systems are presented. Left column shows all system filters, including feedback filter (dashed line) in the time domain. Middle column shows the filters in the frequency domain and right column shows the ROC plots of the models. All these models were found to have significant predictive power in Monte Carlo tests.

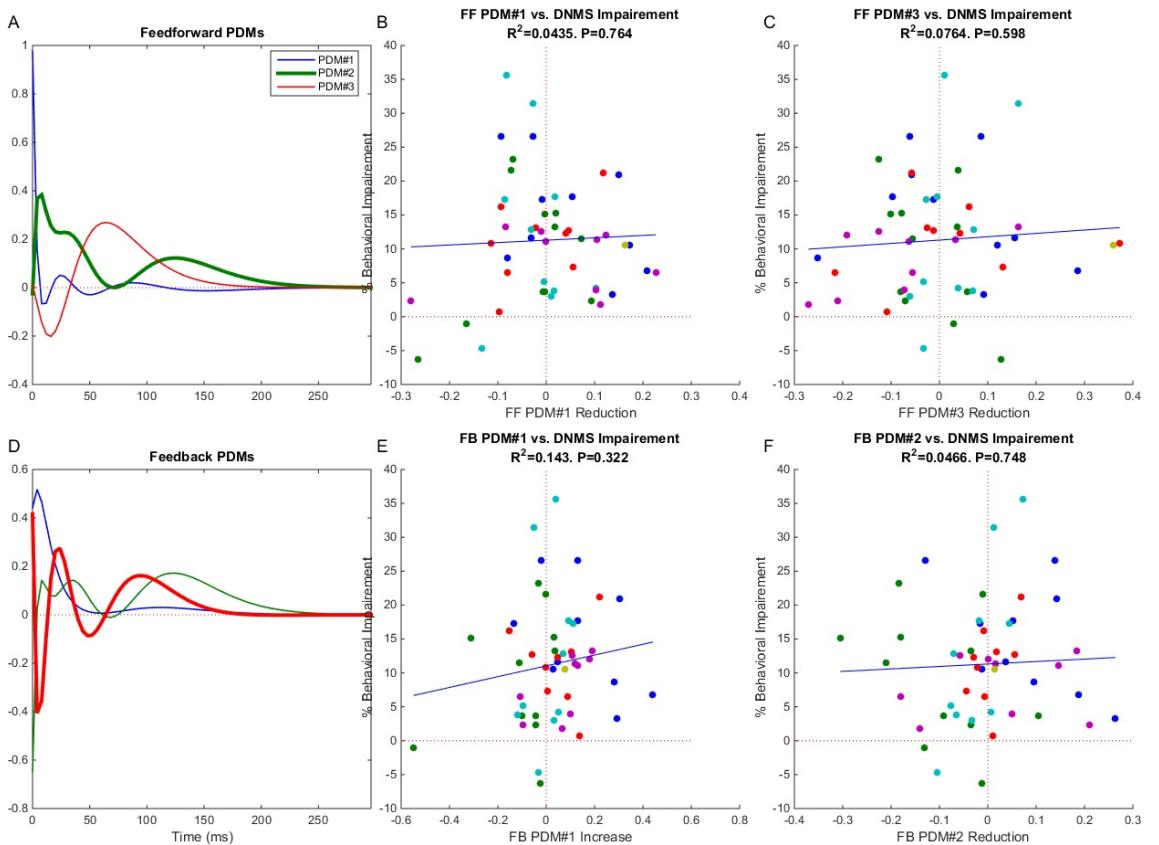


Figure S6: Top Row: neither the first (middle column) nor third feedforward gPDM were found to be significantly correlated with THC induced behavioral deficits. Bottom Row: neither the first (middle column) nor second feedback gPDM were found to be significantly correlated with THC induced behavioral deficits. Format is same as Fig. 3.

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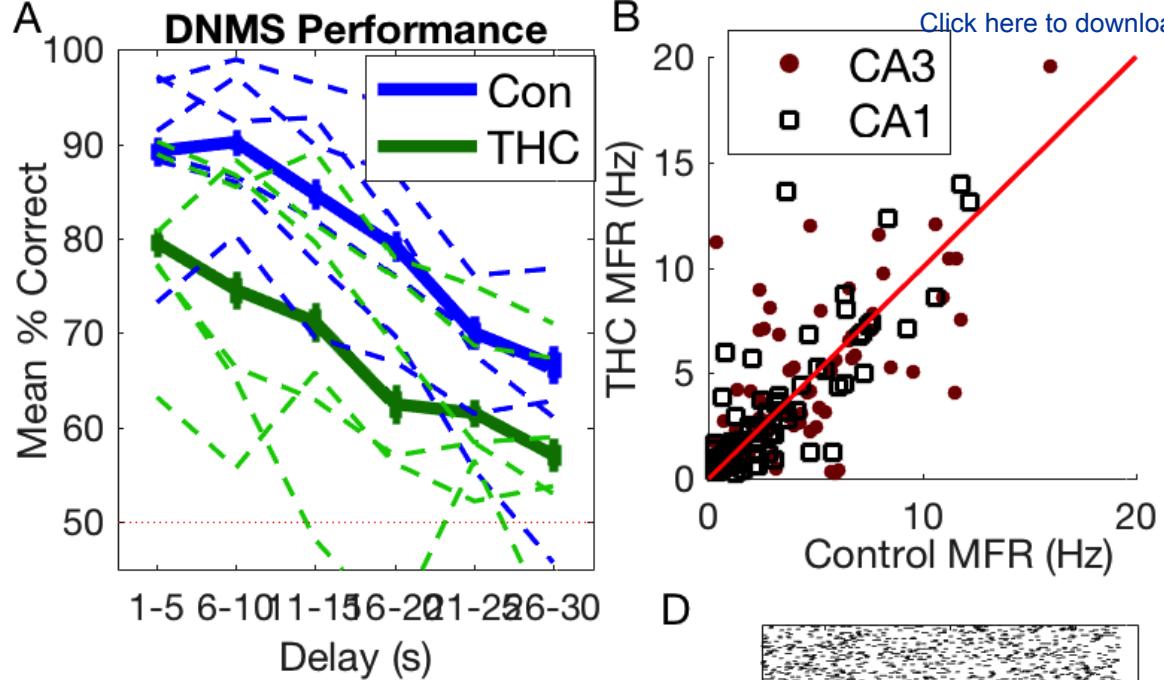
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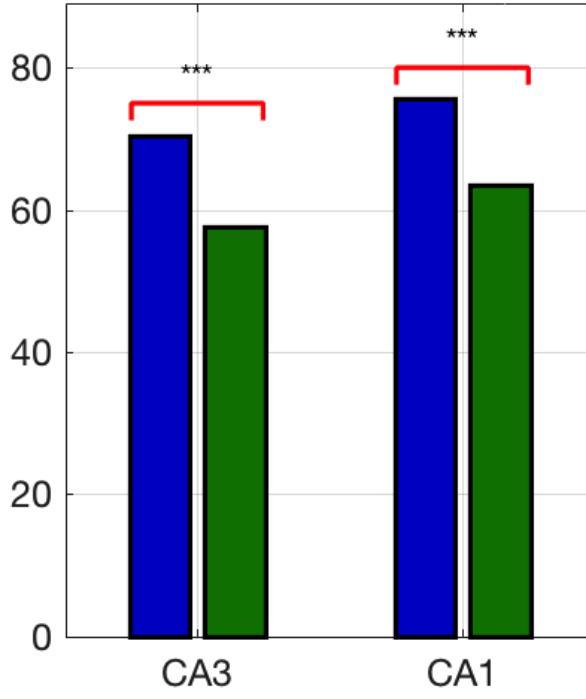
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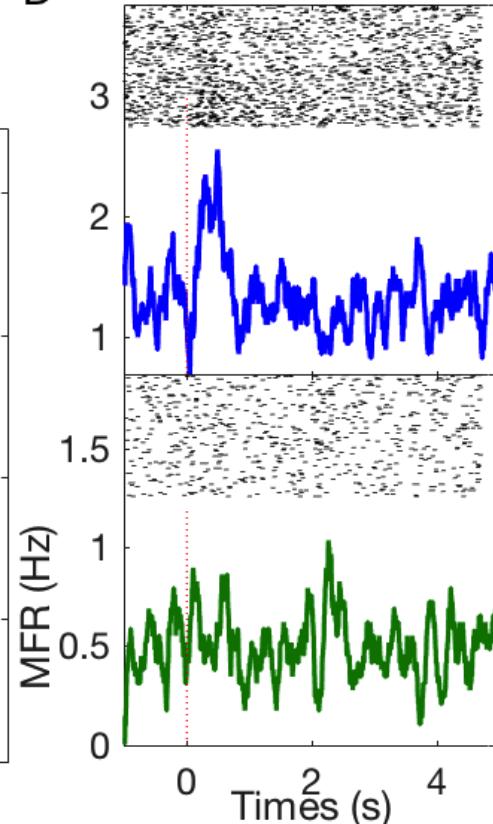
CA3
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C

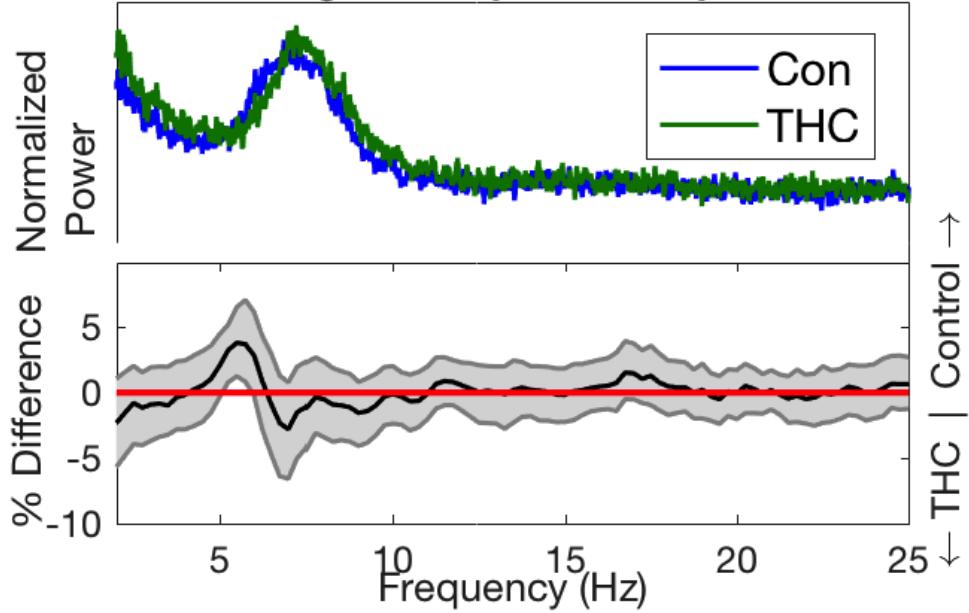
SPC Proportion (%)

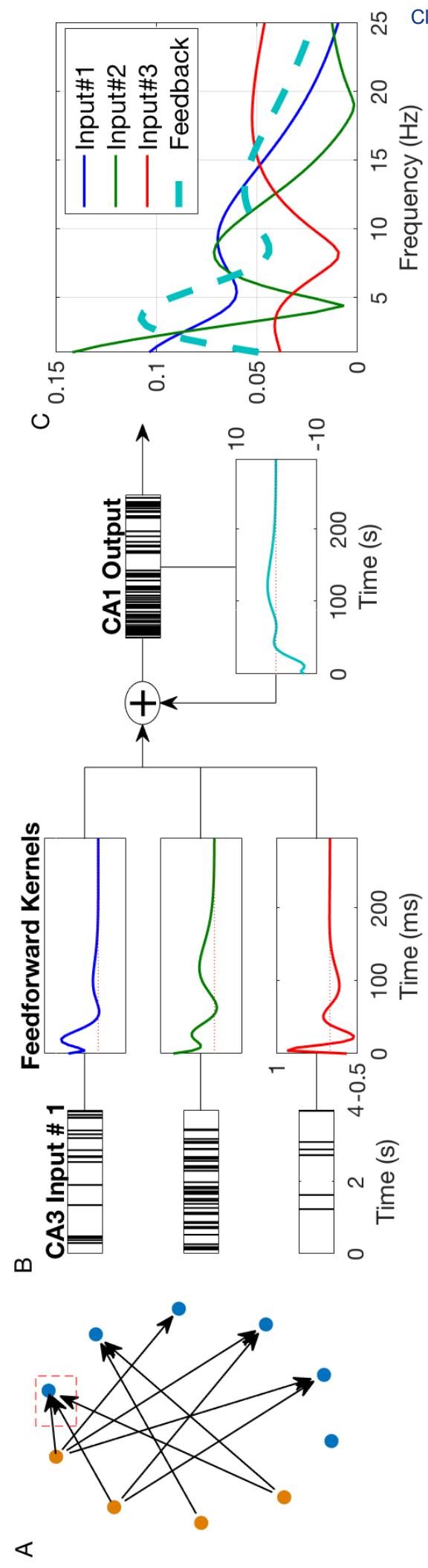


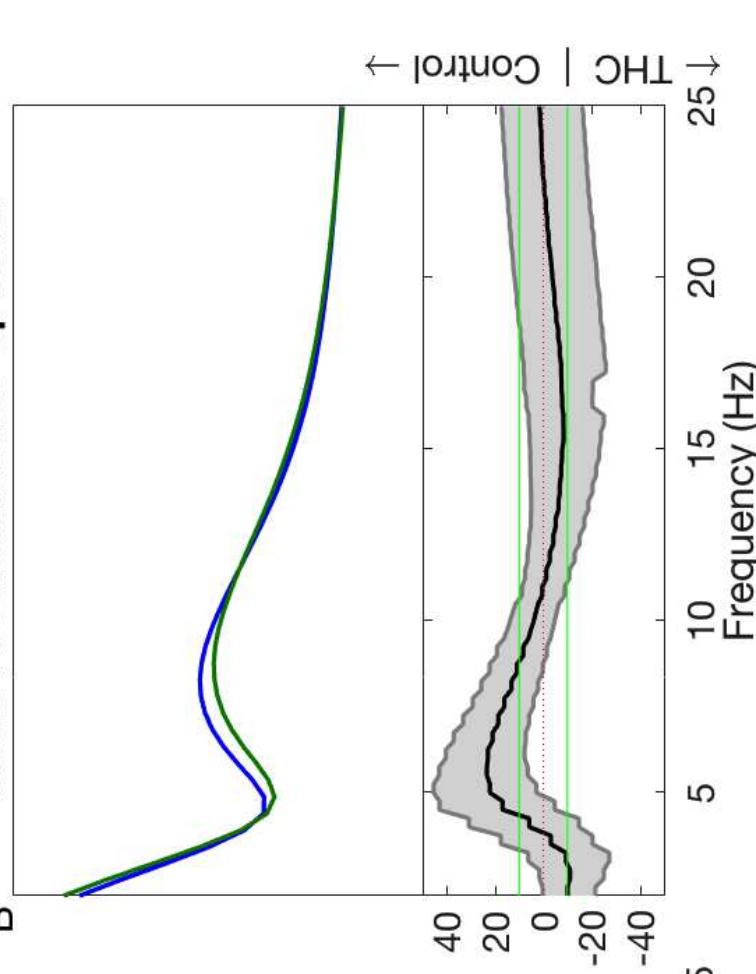
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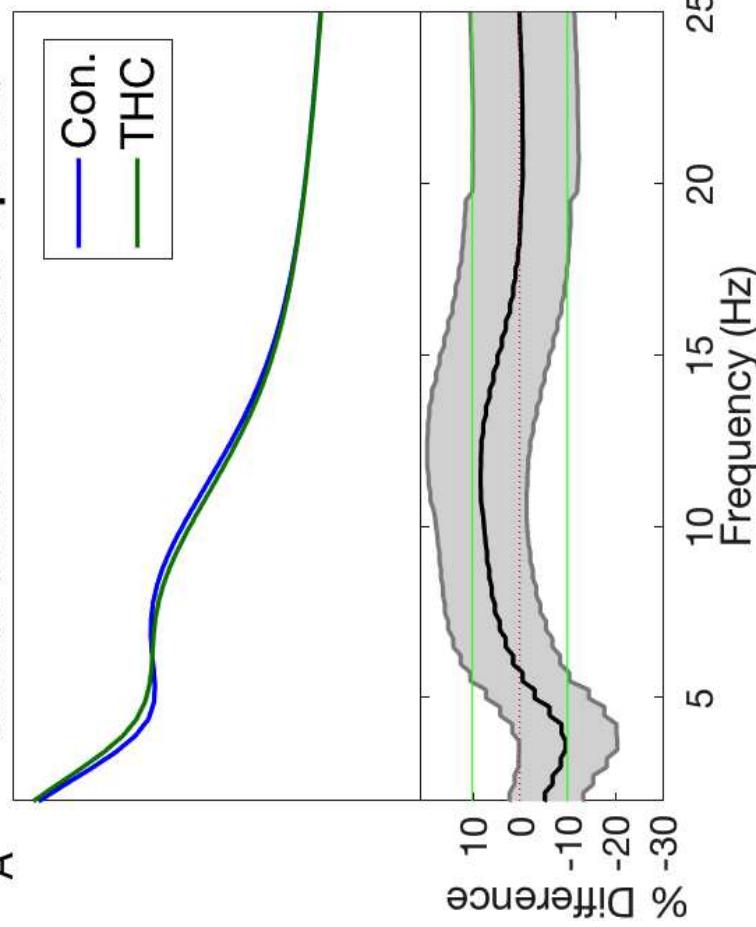
E Average CA1 Spiketrain Spectra



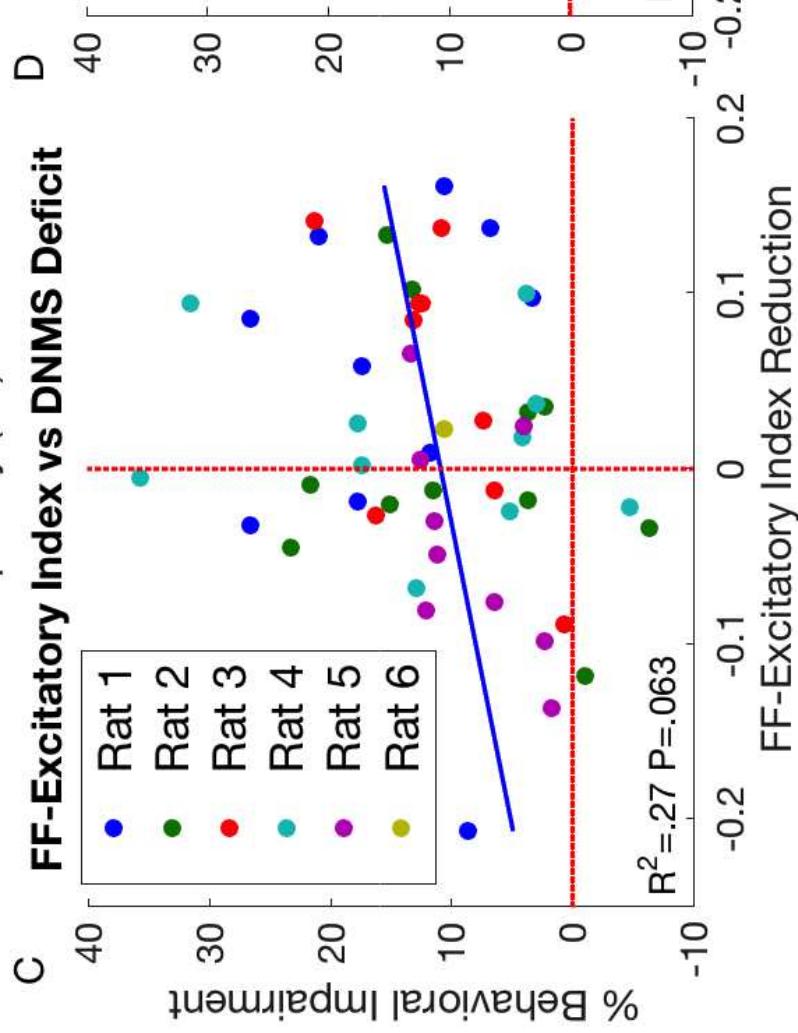
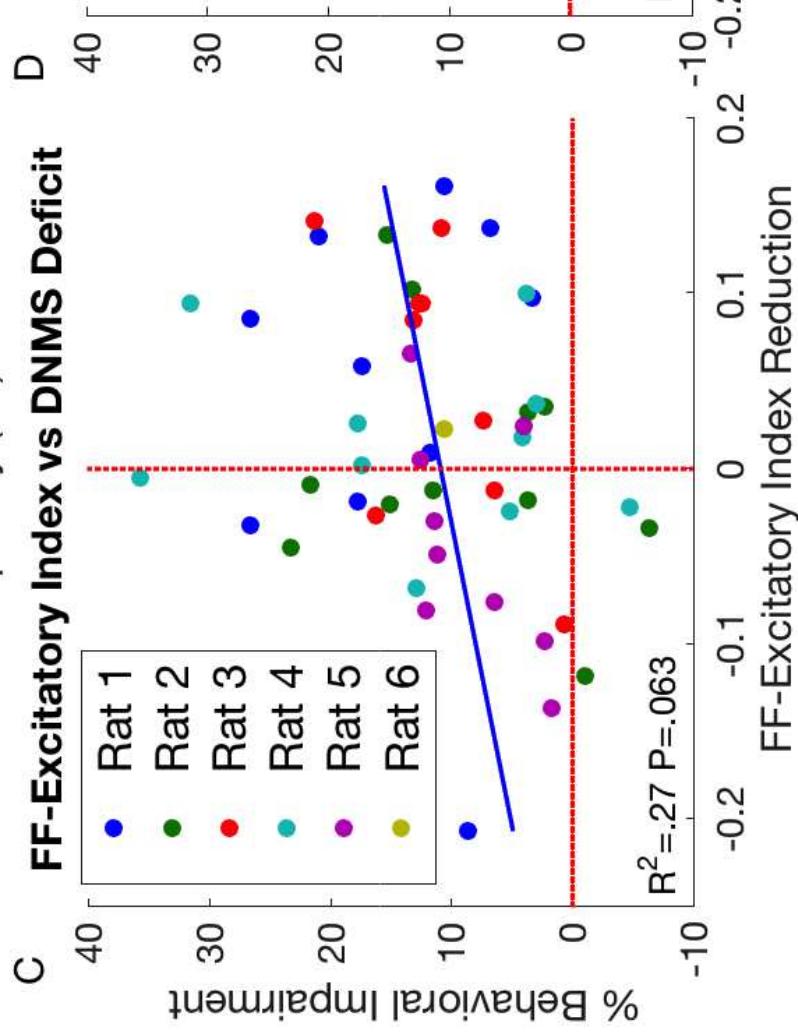


Mean Feedback Filter Spectra

B

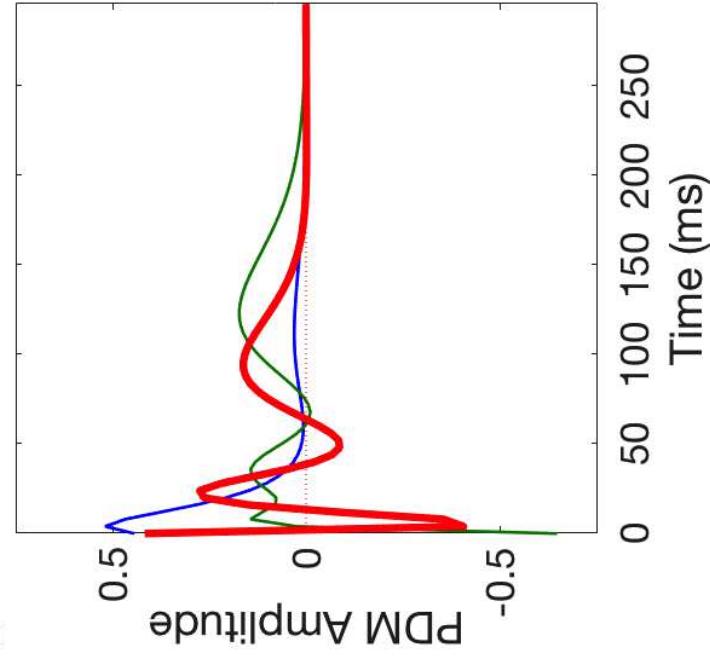
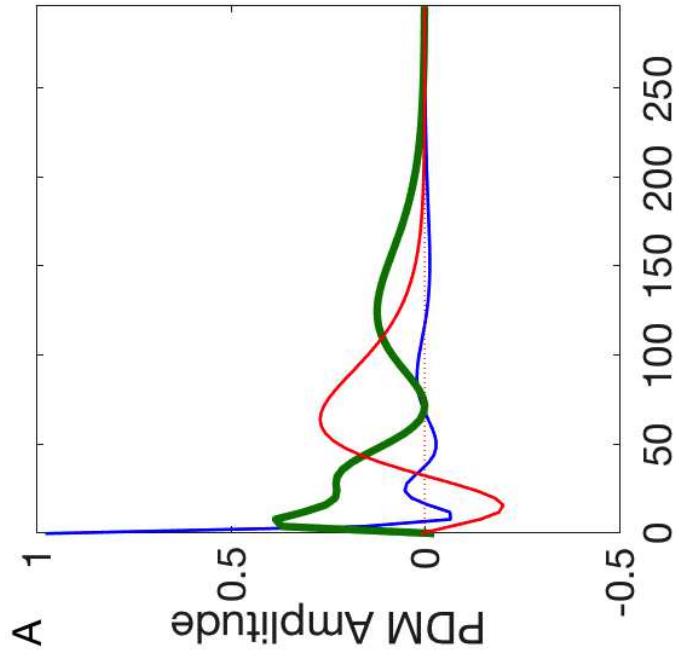
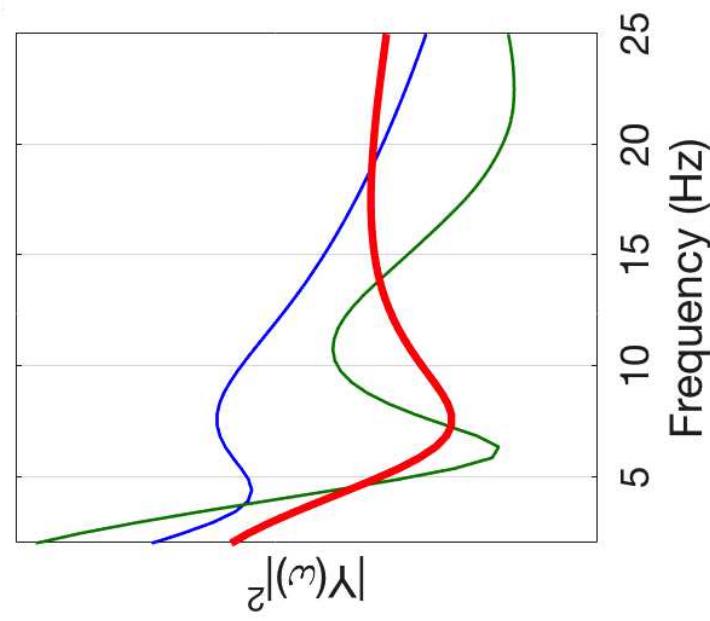
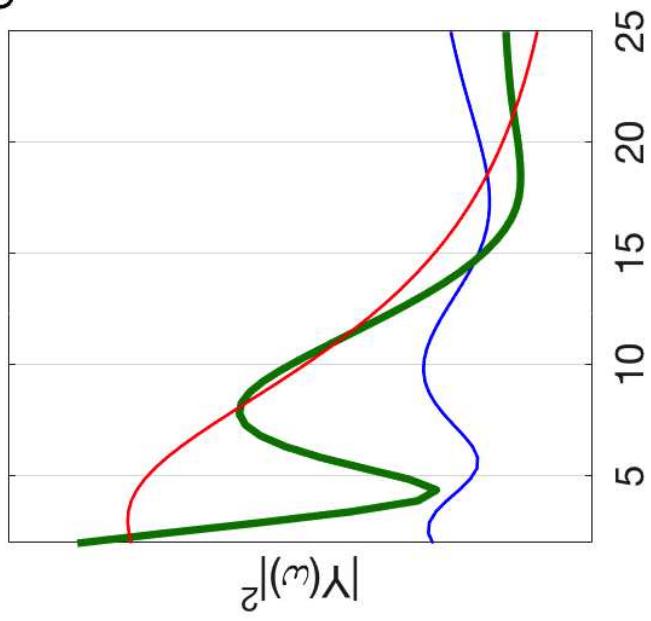
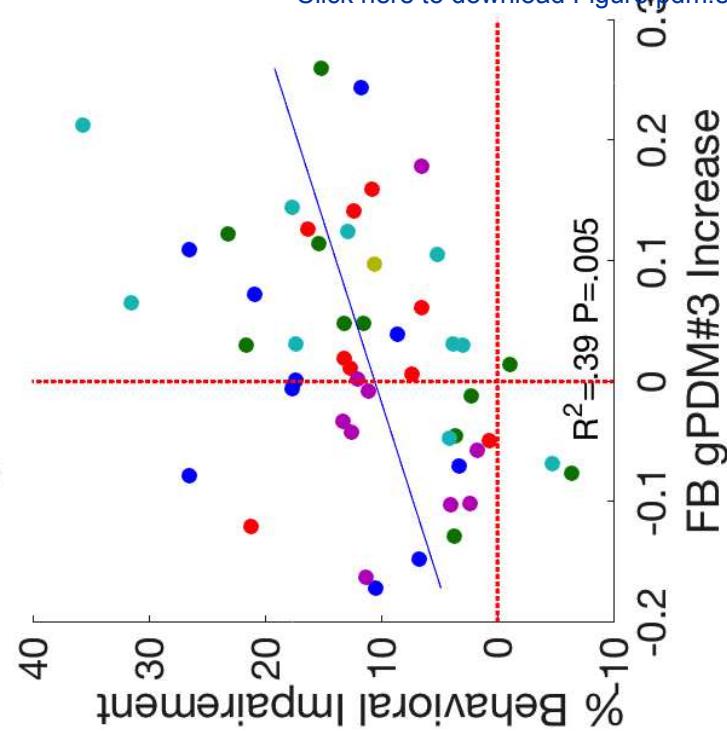
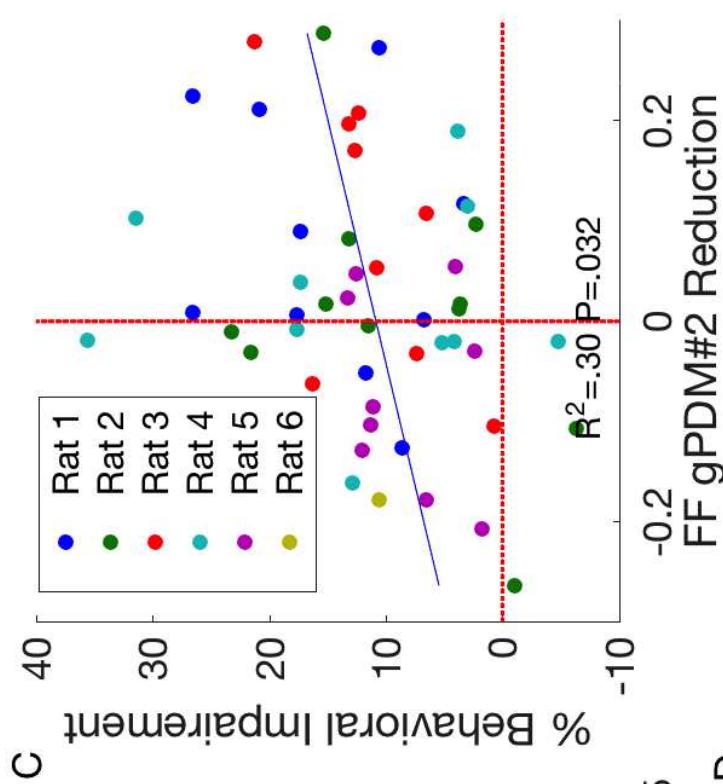
Mean Feedforward Filter Spectra

A

FB-Excitatory Index vs DNMS Deficit**FF-Excitatory Index vs DNMS Deficit**

C

D





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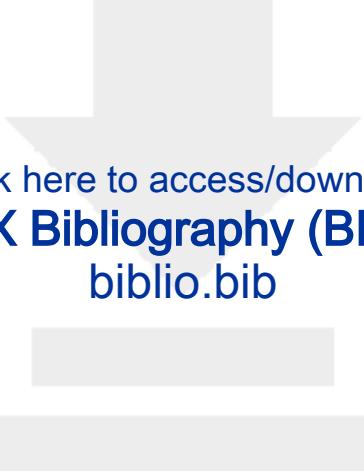
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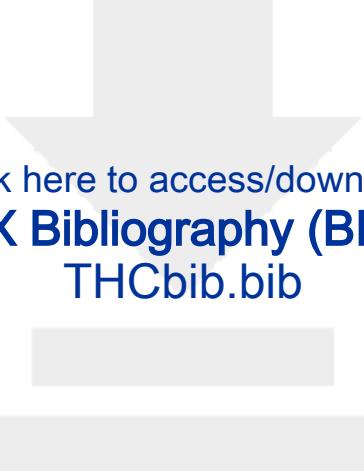
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