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BENEDITO ALVES DE OLIVEIRA JÚNIOR

Investigação da modulação dopaminérgica na sincronia da atividade oscilatória da circuitaria hipocampo-córtex pré-frontal

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Dissertação apresentada à Faculdade de Medicina de Ribeirão Preto da Universidade de São Paulo, como parte das exigências para a obtenção do título de Mestre em Ciências

Área de concentração: Neurociências

Orientador: Prof. Dr. Rafael Naime Ruggiero

Coorientador: Prof. Dr. João Pereira Leite

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“It is change, continuing change, inevitable change, that is the dominant factor in society today. No sensible decision can be made any longer without taking into account not only the world as it is, but the world as it will be”

Isaac Asimov

Resumo

Oliveira Júnior, B. A. **Investigação da modulação dopaminérgica na sincronia da atividade oscilatória da circuitaria hipocampo-córtex pré-frontal**. Dissertação (Mestrado) – Faculdade de Medicina de Ribeirão Preto, Universidade de São Paulo, Ribeirão Preto, 2022.

Com o desenvolvimento empírico e teórico das neurociências percebe-se uma tendência em compreender o funcionamento cerebral em termos de redes e circuitos de atividade e não mais em regiões isoladas como unidades funcionais. Nesta visão, a unidade funcional que sustenta o comportamento animal é formada por redes dinâmicas entre diferentes regiões cerebrais. É proposto que através da sincronização entre oscilações, regiões distantes podem se comunicar de maneira dinâmica e ajustável por demanda de estímulos externos. Na via hipocampo-córtex pré-frontal (HPC-PFC), é possível observar a modulação dessa sincronia em tarefas comportamentais de memória de trabalho espacial. Apesar de não se saber exatamente quais são os mecanismos que permitem essa modulação, a neurotransmissão dopaminérgica é proposta como um dos possíveis fatores modulatórios. No entanto, não se sabe como os padrões temporais de liberação dopaminérgica modulam a sincronia HPC-PFC ou quais os receptores dopaminérgicos específicos responsáveis pelos efeitos. Nesse contexto, nosso objetivo foi investigar a influência da atividade dopaminérgica na sincronia HPC-PFC e avaliar se os efeitos observados são receptores-específicos. Observamos que a administração i.c.v. de dopamina induz o aumento de oscilações teta e da conectividade funcional HPC-PFC que perdura até 20 minutos após a injeção. Esse efeito não é mimetizado pela atuação inespecífica da apomorfina ou pelos agonistas SKF e Quinpirole, os quais atuam respectivamente sobre os receptores D_1 e D_2. No entanto, observamos um efeito tardio com pico de atividade entre 30 e 40 minutos após a administração de dopamina 100 nmol, apomorfina 0,75 mg/kg e quinpirole em que ocorre o aumento da sincronia HPC-PFC em delta. Em conjunto, esses resultados evidenciam a participação da neurotransmissão dopaminérgica na regulação das dinâmicas oscilatórias HPC-PFC, induzindo sincronia em diferentes bandas de frequência via receptores específicos.

Palavras-chave: Dopamina, dinâmica oscilatória neural, conectividade neural, córtex pré-frontal, hipocampo, área tegmental ventral, potencial de campo local, assembleias neuronais, eletrofisiologia.

Abstract

Oliveira Júnior, B. A. **Investigation of dopaminergic modulation in the synchrony of oscillatory activity of the hippocampal-prefrontal cortex circuitry**. Dissertation (Master's degree) – Faculdade de Medicina de Ribeirão Preto, Universidade de São Paulo, Ribeirão Preto, 2022.

Given the theoretical and empirical development of neurosciences, there is a trend to understand brain function in activity of networks and circuits and no longer in isolated regions as functional units. In this view, dynamic networks between different brain regions form the functional unit that sustains animal behavior. It is proposed that oscillatory synchronization promotes dynamical communication that is adjustable to the demand of external stimuli. In the hippocampus-prefrontal cortex (HPC-PFC) pathway, it is possible to observe the modulation of this synchrony in spatial working memory tasks. Although the exact mechanisms that allow this modulation are unknown, dopaminergic neurotransmission is proposed as one of the possible modulatory factors. However, it is not known how temporal patterns of dopaminergic release modulate HPC-PFC synchrony or which specific dopaminergic receptors are responsible for the effects. In this context, our objective was to investigate the influence of dopaminergic activity on HPC-PFC synchrony and to assess whether the observed effects are receptor-specific. We observed that the i.c.v. injection of dopamine induces an increase in HPC-PFC theta oscillations and functional connectivity that lasts up to 20 minutes after injection. This effect is not mimicked by the non-specific action of apomorphine or by the agonists SKF and quinpirole, which act respectively on D_1 and D_2 receptors. However, we observed a late effect with peak activity between 30 and 40 minutes after the administration of dopamine 100 nmol, apomorphine 0.75 mg/kg, and quinpirole in which the HPC-PFC synchrony increased in delta. Together, these results evidence the participation of dopaminergic neurotransmission in regulating HPC-PFC oscillatory dynamics, inducing synchrony in different frequency bands via specific receptors.

Keywords: Dopamine, oscillatory neural dynamics, neural connectivity, prefrontal cortex, hippocampus, ventral tegmental area, local field potential, neuronal ensembles, electrophysiology.

Lista de Abreviaturas e Siglas

APO	Apomorfina
DA	Dopamina
QUIN	Quinpirole
PFC	Córtex pré-frontal
PFCm	Córtex pré-frontal medial
HPC	Hipocampo
HPCd	Hipocampo dorsal
VLD	Ventrículo lateral direito
VTA	Área tegmental ventral
CA1	*Cornu Ammonis* 1 – Seção do hipocampo dorsal
i.p.	Intraperitoneal
i.c.v.	Intracerebroventral
Nmol	Nanomol
µg	Micrograma
mg	Miligrama
kg	Quilograma
Hz	Hertz
Min	Minutos
ACT	Ativado (Activated)
DEA	Desativado (Deativated)
TRANS	Transição (Transition)

Sumário

1. Introdução

1.1. A atividade de populações neuronais

Donald Hebb em sua publicação seminal "*The Organization of Behavior*" (Hebb, 1949) foi um dos primeiros autores a sugerir que a organização espaço-temporal da atividade neuronal reflete funcionalmente em processos neurais e no comportamento animal. Atualmente, é conhecido que populações de neurônios se organizam de maneira dinâmica, sustentando atividades neurais como o processamento sensorial e cognitivo, bem como o planejamento motor, e permitindo aos animais experienciar o ambiente e responder de maneira adaptativa às suas demandas. Nesse cenário, um dos objetivos das pesquisas em neurociências é compreender como ocorre a organização e coordenação dinâmica de populações neuronais. Na neurociência de sistemas, a organização e comunicação de populações neuronais é investigada em larga escala com ferramentas eletrofisiológicas que medem as alterações nos potenciais elétricos gerados pelas populações celulares (Buzsáki, 2004).

Nos neurônios, os potenciais elétricos originam-se dos fluxos de corrente elétrica produzida pelo transporte iônico através das membranas celulares (Buzsáki, Anastassiou & Koch, 2012). Flutuações nos potenciais elétricos são captadas por eletrodos posicionados no meio extracelular e servem como medida direta da atividade neuronal na forma de: (1) disparos neuronais (*spikes*) correspondentes principalmente aos potenciais de ação individuais; e (2) potencial de campo local (LFP, do inglês, *local field potential*) resultante da integração do fluxo iônico relacionado a neurônios próximos ao eletrodo e promovido principalmente por correntes pós-sinápticas excitatórias e inibitórias (Buzsáki, Anastassiou & Koch, 2012). A atividade sináptica sincronizada pode se destacar no LFP como um conjunto de ritmos neurais com diferentes frequências centrais (delta: 0.5-4 Hz; teta: 4-8 Hz; alfa: 8-12 Hz; beta: 12-30 Hz; e gama: 30-120 Hz; Harris & Gordon, 2015). As oscilações neurais estão entre os fenômenos mais conservados na evolução dos mamíferos (Buzsáki, Logothetis & Singer, 2013; Buzsáki & Draguhn, 2004), o que sustenta a hipótese de seu papel relevante na coordenação de populações neuronais (Buzsáki & Draguhn, 2004; Harris & Gordon, 2015).

1.2. Sincronia oscilatória e comunicação entre regiões cerebrais

A geração de uma atividade oscilatória no LFP está relacionada com dois aspectos: (1) a orientação espacial dos dipolos elétricos gerados pelas flutuações iônicas transmembrana, dependente portanto da disposição dos diferentes neurônios em uma região; e (2) a atividade sincronizada, isto é, a coordenação temporal de um grupo de neurônios. Ambos os aspectos são substanciais para a composição de assembleias neuronais, redes distribuídas de grupos neuronais cuja atividade é regida por conexões dinâmicas (Buzsáki & Draguhn, 2004). A formação das assembleias ocorre de maneira transiente e acredita-se ser promovida por sincronização entre oscilações de diferentes regiões, sendo este o possível mecanismo de maior eficiência energética para coordenação temporal da atividade neural (Buzsáki & Draguhn, 2004), inclusive entre regiões cerebrais distantes (Harris & Gordon, 2015). As oscilações possibilitam pacotes temporais de transmissão de informação entre grupos neuronais em momentos de maior ou menor estabilidade. Essa transmissão é maximizada em momentos de estabilidade promovidos pela sincronização das oscilações (Fries, 2005). Essa sincronização, que ocorre através de diferentes padrões de acoplamento de fase entre as oscilações, é referida como coerência e tida como uma das principais medida da conectividade funcional entre regiões cerebrais (Gordon, 2011).

Fries (2005; 2015) propôs a hipótese da “comunicação através da coerência”, na qual a coerência é determinante para a comunicação dinâmica e eficiente entre regiões porque implementa uma janela temporal de milissegundos durante a qual ocorre a transferência seletiva de informações entre os grupos neuronais regidos pelas oscilações coerentes. Nesse curto período de tempo, a transmissão pós-sináptica da informação pelo grupo emissor é priorizada frente a outras informações que chegam ao grupo receptor, garantindo a transferência efetiva de informação. Como exemplo, foi mostrado que os neurônios do córtex visual que respondem a um determinado estimulo sensorial sincronizam na frequência da banda gama (Gray et al., 1989). A cada ciclo de gama que se repete, neurônios excitatórios desencadeiam neurônios inibitórios locais durante um período de 3 ms (Buzsáki & Wang, 2012). A inibição da atividade neuronal local permanece até que o ciclo de gama se reinicie promovendo outro período excitatório de 3 ms. A atividade pós-sináptica excitatória somente é

transmitida nesse curto período temporal e é seguida da atividade pós-sináptica inibitória, que impede a influência de outras entradas pós-sinápticas nesse grupo neuronal de destino, tornando a comunicação seletiva (Fries, 2015).

Em uma hipótese que contrapõe a "comunicação através da coerência", Schneider et al. (2020) argumenta que a coerência não é um mecanismo que viabiliza a comunicação entre grupos neuronais, mas um subproduto dessa comunicação. Schneider et al. (2020) apresenta um modelo computacional que prediz a coerência como subproduto da conectividade estrutural dos neurônios e da potência oscilatória entre as regiões. Apesar de estabelecerem relações de causalidade distintas entre coerência e comunicação neuronal, ambas as hipóteses (Fries, 2005, 2015; Schneider et al., 2020) reconhecem que a coerência não é um processo fixo, mas é variável e ajustável dependendo do estado comportamental e da dinâmica cognitiva. Dentre os processos neurofisiológicos que podem estar relacionados à esse ajuste flexível e dinâmico da coerência neuronal destaca-se a modulação por neurotransmissores que podem modificar a comunicação inter-regiões em diferentes escalas temporais (Ruggiero et al., 2021). A dopamina é um dos neurotransmissores mais estudados e de maior relevância para aspectos cognitivos. De fato, é conhecido que a participação dopaminérgica na dinâmica cognitiva é expressiva (Takahashi et al., 2008; Floresco, 2013; Ott & Nieder, 2019), e está relacionada por exemplo a processos memória de trabalho (D'Ardenne et al., 2012; Chudasama & Robbins, 2004; Duvarci et al., 2018), tomada de decisão (Park & Moghaddam, 2017; Verharen et al., 2018), regulação emocional (Schuster et al., 2022) e planejamento motor (Jenkinson & Brown, 2011). Importante para o papel da dopamina na dinâmica cognitiva é a relação direta que tem sido observada entre a manipulação de receptores dopaminérgicos D_1 e D_2 e a consequente modulação da sincronia oscilatória entre hipocampo (HPC) e córtex pré-frontal (PFC, do inglês, Prefrontal cortex) (Xu et al., 2016; Perreault et al., 2017 Gener et al., 2019). Essa relação tem reforçado a proposta da dopamina como modulador de sincronia neural (Beeler & Dreyer, 2019).

1.3. Sincronia hipocampo-córtex pré-frontal

HPC e PFC são regiões amplamente estudadas pelo seu papel em aspectos cognitivos. Essas regiões se conectam anatomicamente por projeções monossinápticas

e glutamatérgicas do HPC (Hoover & Vertes, 2007). Dado que o PFC é implicado em funções executivas, atenção e comportamentos orientados ao objetivo, e o HPC a aprendizado, memória e navegação espacial, a atividade em rede HPC-PFC é essencial para os processos como memória de trabalho espacial e tomada de decisão (Sigurdsson & Duvarci, 2016; Spellman et al., 2015). A atividade do circuito HPC-PFC é sustentada pela sincronia oscilatória coordenada pela frequência teta hipocampal. (Benchenane et al., 2011). Em roedores, a performance em tarefa dependente da memória de trabalho espacial é correlacionada à sincronia HPC-PFC em teta (Benchenane et al., 2010; Sigurdsson et al., 2010; Fujisawa & Buzsáki, 2011; O'Neill et al., 2013). Nesta tarefa, realizada em um labirinto em T, o aumento na coerência e na potência HPC-PFC ocorre durante deslocamento do animal no braço central do labirinto e atinge o pico no ponto de tomada de decisão (Benchenane et al., 2010; Fujisawa & Buzsáki, 2011). É indicado que essa coerência em teta prediz a escolha do animal pelo braço do labirinto contendo a recompensa, uma vez que ela se correlaciona ao nível elevado de desempenho na tarefa e é também maior quando o animal já atingiu o critério da tarefa (Benchenane et al., 2010; Sigurdsson et al., 2010; Fujisawa & Buzsáki, 2011; O'Neill et al., 2013).

Além da atividade em rede HPC-PFC predominada pelo teta hipocampal, outras dinâmicas oscilatórias estão presentes nas interações HPC-PFC. Nosso grupo (Ruggiero et al., 2018; Lopes-Aguiar et al., 2020; Ruggiero et al., 2021) recentemente descreveu essas dinâmicas oscilatórias distintas entre o HPC e o PFC em ratos anestesiados com uretana caracterizando-as como dois macroestados oscilatórios: o estado desativado, no qual predominam ritmos lentos de potência elevada no mPFC, similar ao padrão oscilatório do sono de ondas lentas; e o estado ativado, caracterizado pelas oscilações teta hipocampais que se assemelham à atividade do sono REM. No estado desativado, as oscilações delta tálamo-corticais coordenam a atividade hipocampal, enquanto no estado ativado, ocorre a sincronização na banda teta no PFC coordenada pela atividade hipocampal. Assim, as transições entre os estados oscilatórios são acompanhadas por mudanças nos padrões de sincronia e se assemelham à alternância entre sono REM e NREM (Lopes-Aguiar et al., 2020).

Em roedores, durante anestesia de uretana, Gretenkord et al. (2019) mostrou que a transição entre estados do sono pode ser evocada por estimulação elétrica da área tegmental ventral (VTA, do inglês, ventral tegmental area), a principal fonte dopaminérgica mesencefálica (Morales & Margolis, 2017). A transição é marcada pela alteração na dinâmica oscilatória do PFC regulada por receptores dopaminérgicos D_1, e é observada também durante sono natural (Gretenkord et al., 2019). Também foi mostrado que a depleção aguda de dopamina suprime parcialmente o sono de ondas lentas e totalmente o sono REM, sendo este último recuperado pela injeção sistêmica de agonistas de receptores dopaminérgicos D_2, mas não D_1 (Dzirasa et al., 2006). Por outro lado, a hiperatividade dopaminérgica gera um estado de vigília específico, cujo padrão de atividade hipocampal se assemelha ao padrão de atividade do sono de ondas lentas (Dzirasa et al., 2006). É sugerido, portanto, que os estados oscilatórios que integram o sistema sono-vigília são regulados pela neurotransmissão dopaminérgica (Dzirasa et al., 2006) possivelmente proveniente da VTA (Gretenkord et al., 2019; Eban-Rothschild et al., 2016; Taylor et al., 2016).

1.4. Dopamina na via meso-cortico-límbica

A dopamina atua amplamente nas vias mesocortical e mesolíbica por meio de duas classes de receptores dopaminérgicos: receptores tipo-D_1 (D_1 e D_5), e receptores tipo-D_2 (D_2, D_3 e D_4). Nessas vias neurais, receptores D_1/D_5 e D_2 são alvos abundantes de dopamina e, em geral, promovem excitabilidade celular e disparos neuronais pela ativação de canais de potássio (K+) e liberação de íons cálcio (Ca2+) intracelulares (Hoffman & Johnston, 1999; Lezcano & Bergson, 2002), enquanto diminuem a excitabilidade pela redução dos picos de corrente dos canais de sódio (Na+) (Cantrell et al., 1999). No PFC, em neurônios piramidais e interneurônios, o agonismo de receptores D_1 promove aumento no potencial de membrana e excitabilidade, elevando o número de disparos neuronais (Yi et al., 2013; Anastasiades, Boada & Carter, 2019), enquanto o antagonismo deste receptor promove o efeito inverso (Yi et al., 2013; Anastasiades, Boada & Carter, 2019). Diferentemente, não há consenso sobre os efeitos do agonismo de receptores D_2, ambos os efeitos de aumento e redução de excitabilidade neuronal são reportados na literatura (Tseng & O'Donnell, 2004; Robinson & Sohal, 2017). No HPC, o agonismo de receptores D_1 promove

excitabilidade (Hamilton et al, 2010) e aumento na frequência de disparos neuronais (Wei et al., 2018). Por outro lado, o agonismo de receptores D_2 produz redução na frequência de disparos em CA1 (Wei et al., 2018), mas aumento de excitabilidade e frequência de disparo no giro denteado revertidos por antagonista D_2 (Etter & Krezel, 2014). A neurotransmissão dopaminérgica também promove alterações na amplitude de potenciais excitatórios pós-sinápticos, regulando diferencialmente a plasticidade sináptica HPC-PFC através de receptores D_1 e D_2 (Gurden, Takita & Jay, 2000; Goto & Grace, 2005, 2008; Xu et al., 2016). Nesse cenário, é estabelecido que processos cognitivos como aprendizado espacial, memória de trabalho e tomada de decisão são sensíveis a alterações na dinâmica de dopamina em receptores D_1 e D_2 mesocorticais (Seamans, Floresco & Phillips, 1998; Wilkerson & Levin, 1999; Onge, Abhari & Floresco; 2011), ilustrando o papel crítico da dopamina para a cognição.

A VTA é a principal fonte de dopamina mesolímbica, com projeções dopaminérgicas abundantes para o PFC (Thierry et al., 1973; Van Eden et al., 1987; Beyer et al., 2015). Nessa região, as fibras dopaminérgicas inervam mais intensamente a região medial, envolvendo as sub-regiões pré-límbica e infra-límbica (Van Eden et al., 1987) e se relacionam funcionalmente aos processos de memória de trabalho (D'Ardenne et al., 2012; Chudasama & Robbins, 2004; Duvarci et al., 2018) e tomada de decisão (Park & Moghaddam, 2017; Verharen et al., 2018). No HPC, os terminais dopaminérgicos da VTA são amplamente distribuídos (Scatton et al., 1980; Gasbarri et al., 1994; Luo et al., 2011; Kempadoo et al., 2016; Adeniyi, 2020), se estendendo ao longo das subregiões *stratum oriens* e *stratum reticulatum*, principalmente pelo hilo do giro denteado, a camada piramidal de CA3 e os dendritos basais de CA1 (Adeniyi et al., 2020). Funcionalmente, a dopamina no HPC tem se mostrado importante no controle do fluxo de informação (Rosen et al., 2015), na promoção de memória espacial (McNamara, 2014) e memória de trabalho espacial (Martig et al., 2009), e na persistência da memória de longo prazo (Rossato, et al. 2009).

Baseado na relação da dopamina com a predição de recompensas, e na possibilidade desse neurotransmissor produzir alterações de plasticidade sináptica na via HPC-PFC (Gurden et al., 2000) e induzir sincronização neuronal cortical quando aplicado em conjunto com NMDA em *slices* (Gireesh & Plenz, 2008), Benchenane et al. (2010) hipotetizou que a dopamina pode participar da sincronização HPC-PFC. Em

ratos anestesiados, Benchenane et al. (2010) infundiu dopamina no PFC e observou aumento da coerência espectral em teta na via HPC-PFC, reproduzindo o mesmo padrão de coerência observada quando o rato atingia o ponto de tomada de decisão durante o teste comportamental. Posteriormente, Fujisawa & Buzsáki (2011) revelaram que a atividade oscilatória sincronizada entre HPC e PFC durante a tomada de decisão no teste comportamental abrange também a VTA, na qual é originado um ritmo de 4 Hz que sincroniza a atividade das três regiões. O 4 Hz é predominante na via VTA-PFC e juntamente com o teta hipocampal coordena através de acoplamento de fase as oscilações gama locais e a formação das assembleias neuronais em cada região. De maneira similar a Benchenane (2010), Fujisawa & Buzsáki (2011) hipotetizam que a dopamina tem participação na sincronia VTA-HPC-PFC, e que a atividade dos neurônios dopaminérgicos da VTA pode ser a origem do 4 Hz.

Em conjunto, a literatura indica que a neurotransmissão dopaminérgica modula a comunicação límbico-cortical e a performance cognitiva subjacente através de sincronia entre assembleias neuronais. Esses resultados evidenciam também o papel dopaminérgico na sincronização neuronal em diferentes escalas temporais. Sugere-se ainda que as propriedades modulatórias da dopamina são determinante na regulação dos estados oscilatórios que integram o sistema sono-vigília. No entanto, a participação dopaminérgica e seu mecanismo de atuação nesses processos não são bem estabelecidos na literatura e permanecem pouco compreendidos. Até o momento, somente o papel dopaminérgico da VTA sobre o PFC tem sido investigado com ferramentas de alta precisão espaço-temporal ou seletividade celular, como optogenética e DREADDS (Designer Receptors Exclusively Activated by Designer Drugs). Como exemplo, Duvarci et al. (2018), utilizando camundongos na tarefa do labirinto em T, investigaram a associação entre a atividade de neurônios dopaminérgicas da VTA e o desempenho na tomada de decisão baseada em memória de trabalho. Foi observado que camundongos com maior número de escolhas corretas apresentaram a ocorrência de sincronia VTA-PFC com aumento da potência na frequência de 4 Hz durante a tomada de decisão. No entanto, camundongos geneticamente modificados com sinalização dopaminérgica prejudicada não apresentaram sincronia em 4 Hz e tiveram um prejuízo no desempenho da tarefa. Apesar deste resultado ilustrar a necessidade da sinalização dopaminérgica para a

sincronia da via VTA-PFC e o desempenho cognitivo, não foi revelado como padrões diferentes de sinalização dopaminérgica afetaria a comunicação da via e o comportamento animal. Lohani et al. (2019) exploram parcialmente essa questão com ratos em livre movimento. Em seu estudo, os autores geram optogeneticamente diferentes padrões de atividade nos neurônios dopaminérgicos da VTA e observam uma modulação dopaminérgica das oscilações no PFC em escalas temporais distintas. Similarmente, mas utilizando optogenética em *slices* cerebrais de ratos, Zhong et al., (2020) ativaram de maneira breve ou prolongada a VTA. Foi observado que a ativação breve da VTA promove disparos neuronais imediatos no PFC mediados pelo sistema glutamatérgico. Por outro lado, a ativação prolongada promove no PFC a excitação gradual de interneurônios GABAérgicos e a excitação breve de neurônios principais por influência de receptores dopaminérgicos de tipos- D_1 e D_2. O estudo indica que os neurônios dopaminérgicos da VTA influenciam a atividade unitária do PFC principalmente por interneurônios inibitórios e que essa influência depende de uma atividade prolongada da VTA.

Apesar de suas contribuições, os estudos resumidos no parágrafo anterior se restringem a investigar os efeitos da dopamina no PFC, e não englobam o HPC, ainda que a atividade coordenada entre as ambas as regiões seja crítica para a tomada de decisão e a memória de trabalho espacial (Fujisawa & Buzsáki, 2011; Benchenane et al., 2010). Neste estudo, propusemos investigar e caracterizar a atividade dopaminérgica na regulação da dinâmica oscilatória HPC-PFC com a precisão da resolução temporal da eletrofisiologia. Nosso objetivo foi avaliar como a neurotransmissão dopaminérgica modula a sincronia e as dinâmicas oscilatórias mesocorticais em resposta a demandas comportamentais e cognitivas. Com base na hipótese da “comunicação através da coerência” (Fries, 2005; 2015), e nas evidências experimentais que sugerem a dopamina como fator modulatório da coerência oscilatória, nossa hipótese é de que a dopamina atua no ajuste dinâmico da sincronia em estruturas límbico-corticais.

2. Objetivos

2.1. Objetivos gerais

O objetivo principal deste estudo foi investigar a participação da neurotransmissão dopaminérgica na atividade oscilatória da via HPC-PFC e se os efeitos produzidos pela dopamina são específicos de receptores dopaminérgicos D_1 ou D_2. Para isso, avaliamos os potenciais de campo local HPC-PFC durante a administração de dopamina ou dos agonistas dopaminérgicos apomorfina, SKF e Quinpirole em concentrações distintas.

2.2. Objetivos específicos

a) Investigar os efeitos do agonismo inespecífico da apomorfina sobre os estados oscilatórios, a potência e a sincronia HPC-PFC, e se os efeitos variam em função das concentrações de 0.75 mg/kg, 1.5 mg/kg e 3 mg/kg da droga.

b) Caracterizar os efeitos da dopamina exógena sobre os estados oscilatórios, a potência e a sincronia HPC-PFC, e se os efeitos variam em função das concentrações de 500 nmol e 100 nmol do neurotransmissor.

c) Identificar os efeitos dos agonistas seletivos SKF (receptores D_1) e Quinpirole (receptores D_2) sobre os estados oscilatórios, a potência e a sincronia HPC-PFC, e se os efeitos variam em função das concentrações de 1 µg e 10 µg das drogas.

3. Resultados

3.1. Artigo científico

Investigation of dopaminergic modulation in the synchrony of oscillatory activity of the hippocampal-prefrontal cortex circuitry

Abbreviated title: Dopaminergic modulation of HPC-PFC oscillatory synchrony

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Conflict of interest

The authors declare no competing financial interests.

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Abstract

Interaction between brain networks form the functional unit that sustains cognition and behavior. It has been proposed that oscillatory activity can synchronize distant neuronal populations. One crucial aspect to elucidate brain function and its emergent properties is to understand how functional connectivity is modulated in different time-scales according to environmental or physiological demand. Modulatory neurotransmitters such as dopamine has been implicated in changes in membrane excitability, modulation of oscillatory power and coherence in crucial circuits for cognition such as the hippocampus-prefrontal cortex (HPC-PFC) pathway. However, it is not known how dopaminergic release modulate specifically the phase synchrony of HPC-PFC or which specific dopaminergic receptors are responsible for the effects. In this context, our objective was to investigate the influence of dopaminergic activity on HPC-PFC synchrony and to assess whether the observed effects are receptor-specific. Our results show that dopamine induces HPC-PFC theta synchrony dose-dependently. This effect is not reproduced by apomorphine unspecific agonism or by SKF and quinpirole agonists, which act respectively on D_1- and D_2-like receptors. Additionally, we observed a late effect with peak activity between 30 and 40 minutes after dopamine 100 nmol, apomorphine 0.75 mg/kg, or quinpirole administration in which the HPC-PFC delta synchrony increased. Together, these results evidence the participation of dopaminergic neurotransmission in regulating HPC-PFC oscillatory dynamics, Influencing the synchronization in slow frequency oscillation and long-distant brain communication.

Keywords: Dopamine, oscillatory synchrony, neural connectivity, prefrontal cortex, hippocampus, ventral tegmental area, local field potential, neuronal ensembles.

Introduction

The brain activity underlying animal behavior is highly flexible and distributed among neuronal networks. Neural oscillations are believed to promote the formation of neuronal ensembles and facilitate communication between ensembles from distinct brain regions (Fries, 2005; Buzsáki, 2010). Oscillations are possibly the most energy-efficient mechanism for the temporal coordination of neural activity (Buzsáki & Draguhn, 2004). Therefore, investigating how the oscillatory synchrony mechanism works is especially interesting in understanding the dynamic coordination of brain activity.

In a hypothesis entitled "communication through coherence", Fries (2005; 2015) proposes that coherence, a measure of synchrony, is crucial for dynamic and selective communication between brain regions. This functional communication would be possible because coherence implements a milliseconds time window during which the selective transfer of information between neuronal groups governed by coherent oscillations occurs. During this period, the postsynaptic information transmission by the sender group is prioritized over other information arriving at the receiving group, ensuring selective information transfer. Fries (2015) points out that coherence is not a fixed process but variable and adjustable according to behavioral state and cognitive demand. In this sense, two neurophysiological processes possibly related to coherence dynamics are synaptic plasticity (Uhlhaas et al., 2010) and modulatory neurotransmission, among which dopamine stands out (Beeler & Dreyer, 2019). Two regions that exhibit dynamically coordinated activity and are mainly regulated by synaptic plasticity and modulatory neurotransmission are the hippocampus (HPC) and the prefrontal cortex (PFC; Ruggiero et al., 2021).

The HPC and PFC are anatomically connected regions widely studied for their joint role in cognitive functions and emotional processes, as well as their implication in neuropsychiatric disorders (Ruggiero et al., 2021). HPC-PFC interaction is essential for processes such as spatial working memory and decision-making (Sigurdsson & Duvarci, 2016; Spellman et al., 2015) and is supported by hippocampal theta oscillations (Gordon, 2011; Benchenane et al., 2011). Rodent performance on spatial cognition and working memory tasks is correlated with HPC-PFC theta synchrony (Benchenane et al.,

2010; Sigurdsson et al., 2010; Fujisawa & Buzsáki, 2011; O'Neill et al., 2013). Benchenane et al. (2010), using rats in a T-maze task, showed that HPC-PFC theta coherence changes dynamically during animal locomotion in the maze's central arm and peaks at the decision-making point. The increase in HPC-PFC theta coherence predicts correct choices in the maze task (Benchenane et al., 2010; Sigurdsson et al., 2010; Fujisawa & Buzsáki, 2011; O'Neill et al., 2013). Notably, Benchenane et al. (2010) also showed that HPC-PFC theta coherence increase could be reproduced by local dopamine administration in anesthetized rats PFC. It is known that dopamine release in the cortex increases during working memory tasks (Phillips et al., 2004). Furthermore, both agonism and antagonism of D_1- and D_2-like dopamine receptors are associated with changes in HPC-PFC theta coherence (Xu et al., 2016; Perreault et al., 2017; Gener et al., 2019), reinforcing the dopamine proposal as a neural synchrony modulator (Beeler & Dreyer, 2019).

The literature indicates that dopaminergic neurotransmission regulates the HPC-PFC oscillatory activity, mainly influencing power and coherence. (Benchenane et al., 2010; Xu et al., 2016; Perreault et al., 2017; Gener et al., 2019). However, it is not known how dopaminergic release specifically modulates HPC-PFC phase synchrony and whether the effects are receptor-specific. Considering this, we investigated the effects of dopamine administration on HPC-PFC synchrony and whether these effects are reproduced by non-specific apomorphine agonism or selective D_1- and D_2-like dopamine receptors agonism. Our findings reveal that dopamine induces HPC-PFC theta power and synchrony dose-dependently, and this effect is not reproduced by apomorphine or D_1- and D_2-like dopamine receptors agonism. In contrast, dopamine, apomorphine 0.75 mg/kg, and quinpirole induce late HPC-PFC delta synchrony. Therefore, our data suggest that dopaminergic neurotransmission has an essential but complex role in regulating HPC-PFC oscillatory activity, influencing not only power and coherence but also phase synchrony in slow oscillations.

Material and Methods

Animals

Forty-two male Sprague Dawley rats, seven weeks old, were used in the experiments. The animals were housed in standard rodent cages and kept in a controlled-temperature room (24 ± 2 ºC) which operates in cycles of 12 hours of light and 12 hours of dark, with lights on at 7:00 a.m. All animals had ad libitum access to food and water. This study was approved by the local ethics committee on animal experimentation (Ribeirão Preto Medical School, University of São Paulo; protocol number: 74/2021).

Experimental design

Groups were identified according to the drug administered: APO (apomorphine at concentrations of 0.75, 1.5, and 3 mg/kg); DA 500 (dopamine at a concentration of 500 nmol); DA 100 (dopamine at a concentration of 100 nmol); SKF (SKF D_1 agonist at concentrations 1 and 10 µg); and QUIN (D_2 agonist Quinpirole at concentrations 1 and 10 µg). Animals in each group were given a saline injection followed by a random dose of the chosen drug. The interval between injections was at least 60 minutes to avoid or reduce drug influence on the next injection.

Surgery and electrode implantation

Rats were anesthetized under urethane (1.2 mg/Kg in NaCl 0.15 M, i.p.) and placed in a stereotaxic frame (Kopf Instruments, EUA) equipped with a heating pad (Insight, Brazil) for temperature maintenance (37 ± 0.5 °C). Once the skull was exposed, burr holes were drilled, targeted at the left medial PFC (anteroposterior, AP: + 3.2 mm; medial-lateral, ML: - 0.5 mm; dorsal-ventral, DV: - 2.9 mm), the left dorsal HPC (AP: - 5.0 mm, ML: - 2.7 mm, DV: - 3.1 mm) and the right lateral ventricle (LV; AP: - 0.5 mm, ML: - 1.8 mm, DV: - 3.5 mm). Drug infusions were performed via a Hamilton microsyringe (10 µL) connected to a polyethylene tubing and a 30 gauge cannulae at a rate of 0.05 µL/min.

Steretrodes (two 50 µm teflon-coated tungsten wires intertwined) or silicon probes (32-channel acute probe, E64+R-50-S4-L6-200 NT, ATLAS Neuroengineering, Belgium) were implanted in the PFC, and only stereotrodes were implanted in the HPC.

Stereotrodes were attached to silver wires soldered into an 8-channel connector (Omnectics Connector Corporation, EUA). Silicon probes and Omnetics connectors were coupled to a 32-channel Intan headstage preamplifier (Intan Technologies, EUA).

Extracellular recordings

The recordings were acquired using Open Ephys acquisition system (Open Ephys Production Site, EUA). For recordings with silicon probes, the following parameters were used for signal acquisition: 1000× gain, 30 kHz sampling rate, 0.5-7603.8 Hz bandpass filtering. The parameters for recordings with tungsten wire stereotrodes were: 1000× gain , 5 kHz sample rate, 0.1-1000 Hz bandpass filtering.

Drug preparation

Apomorphine Hydrochloride (Sigma, USA), SKF-38393 Hydrochloride (Sigma, USA), and Quinpirole Hydrochloride (Sigma, USA) were directly diluted in saline (0.9% NaCl). Dopamine Hydrochloride (Sigma, USA) was diluted in 0.04 mg/ml Ascorbic Acid solution to prevent oxidation. After dilution, the drugs were preserved in a freezer at -80ºC and thawed once for use.

Brain extraction and tissue processing

At the end of the experiments, the rats anesthetized with urethane were submitted to an electrolytical lesion for histological marking of the electrode insertion sites. Rats were sacrificed with an additional dose of thiopental (25 mg/kg, i.p.). Brains were extracted and preserved in PFA (4%) over 12 hours and then in sucrose (30%) over 72 hours. Histological sections were performed in the semi-frozen brains for staining with hematoxylin and eosin and subsequent verification of the electrode insertion sites.

Data analysis

Signal analyses were performed using custom codes in MATLAB software (Mathworks, EUA). Raw LFP was decimated to 500 Hz.

Classification of oscillatory states under urethane anesthesia

State classification was performed using the method described in Lopes-Aguiar et al. (2020). We divided the recording in 10s epochs for classification. Then we

calculated the root mean square (RMS) and the zero-crossing rate (ZC) for each epoch, which were used as input to a k-means clustering. After k-mean clustering we manually adjusted the limits of the clusters and excluded epochs that were notable outliers in order to clearly divide the epochs tree different states: (1) Deactivated (DEA), in which the epochs exhibit slow oscillations of high amplitude and, therefore, with high RMS value and low ZC value; (2) Activated (ACT), in which predominate fast low-amplitude oscillations evidenced by a low RMS value and a high ZC value; and (3) Transition (TRANS), whose oscillatory patterns are unstable and are confused with the patterns exhibited by the other two states, with average RMS and ZC values.

Spectral power

Power spectral density (PSD) was calculated using Welch's method via the Fast Fourier Transform algorithm available in the MATLAB software. We used 3s time windows with 50% overlap and 2^{16} FFT points. We averaged the PSD estimates across trials and animals, respectively. For statistics, we integrate the powers into specific frequency bands (delta: 0.5-2 Hz, low theta: 3-6 Hz, high theta: 6-10 Hz, low gamma: 30-55 Hz). We calculate the relative power by dividing the PSD estimate by the integrated power over the frequency range of 0.5-55 Hz. For spectrograms of the whole recording, we used the mtspecgramc function from Chronux toolbox (Bokil et al., 2010), using multi-tapered window method (5 tapers of 3 s).

Functional connectivity

Spectral coherence, pairwise phase consistency (PPC; Vinck et al., 2010) and debiased weighted phase lag index (DWPLI; Vinck et al., 2011) measures were estimated using cross PSDs of HPC and PFC calculated using modified Welch's periodogram method. Spectral coherence is the same as that obtained by MATLAB's mscohere function and indicates how well the signals being compared match each other at each frequency. PPC is calculated as described by Vinck et al. (2010) and indicates unbiasedly how similar the relative oscillation phase is between trials. The DWPLI is calculated as described by Vinck et al. (2011) and indicates the phase relationship between the oscillations without interference from volume conduction bias.

For coherograms of the whole recording, we used the cohgramc function from Chronux toolbox (Bokil et al., 2010) with multi-tapered window method and the same parameters described for spectrograms.

Statistical Analysis

We evaluated the residuals, homoscedasticity, probability distribution plots (QQ plots), and the Shapiro-Wilk normality test to verify the data distribution. To compare two experimental groups, we used the paired or unpaired two-tailed Student's T test, or the non-parametric tests Wilcoxon matched-pairs signed rank test or the Mann-Whitney test, respectively. For comparing more than two experimental groups, we used one-way or two-way ANOVA with repeated measures and multiple comparisons with P-value corrected by Tukey's or Bonferroni's post-hoc test. As an alternative to ANOVA, due to the presence of missing values, we used the linear mixed effects model (LMM) with repeated measures and multiple comparisons with p-value corrected by Dunnett's post-hoc test. All statistical analyzes were performed using the GraphPad Prism 9.0 software (GraphPad Software, EUA).

Results

Initially, to evaluate the effects generated by manipulation of dopaminergic receptors on HPC-PFC activity, we performed systemic administration (i.p.) of three different apomorphine doses (0.75, 1.5, and 3 mg/kg) chosen because they are the most frequently used in the literature to produce behavioral effects. We performed the analyzes at three levels, namely: (1) the influence of the drug on the dynamics of the oscillatory states characteristic of urethane anesthesia; (2) the drug's influence on the spectral properties of electrophysiological activity; and (3) the drug's influence on HPC-PFC connectivity.

Dose-dependent changes in the dynamics of oscillatory states after APO administration

APO had a dose-dependent effect on the time proportion of states. The low dose administration (0.75 mg/kg) increased the time proportion of DEA states (t test, $t(3)=5.418$, $p=0.012$; Fig. 2A) while reduced in TRANS states (t test, $t(3)=3.184$, $p=0.049$; Fig. 2A). Similarly, the intermediate dose (1.5 mg/kg) decreased the time

proportion of TRANS states (t test, t(5)= 3.636, p=0.015; Fig 2A). In contrast, the high dose (3 mg/kg) increase time proportion of ACT states (t test, t(4)=3.400, p=0.027; Fig. 2A). In addition, we also evaluated the average time proportion of states, which indicates whether a change in the duration of a state is consistent across occurrences of the respective state. We observed an increase in the average time proportion of DEA states after APO 0.75 mg/kg administration (t test, t(3)=2.872, p=0.063; Fig. 2B) and ACT states after APO 3 mg/kg administration (t test, t(4)=2.565, p=0.062; Fig. 2B). Taken together, these results demonstrate that apomorphine induces a predominance of DEA states at a low dose, and at a high dose, it induces a predominance of ACT states.

Spectral and connectivity changes after APO administration

The spectral activity is also affected in a dose-dependent manner, which is verified by the coherence and power spectrograms, and by the theta/delta ratio (Fig. 3). To investigate whether APO influences HPC-PFC synchrony, we evaluated the spectral coherence of different frequency bands over time to determine the peak effect (Fig. 3E), and performed the PSD of the spectral coherence, comparing the baseline with the period of effect after injection (Fig. 4). Spectral coherence is one of the primary measures used to assess synchrony between two brain regions. However, this measure is considerably dependent on and biased by spectral power. As observed in the literature (Benchenane et al., 2010), an increase in HPC-PFC coherence may occur without necessarily observing an increase in power. In this sense, we also decided to use two phase synchrony measures that are less biased by spectral power, the PPC (Vinck et al., 2010) and the DWPLI (Vinck et al., 2011). We observed that apomorphine 0.75 mg dose shifts brain oscillation to a delta prominent state. There is a reduction in theta/delta ratio and high theta relative power, and an increase in delta coherence. This high theta increase is significant in HPC (t test, t(3)=4.305, p=0.023; Fig. 4A), which presents also an increase in delta relative power (t test, t(3)=2.469, p=0.090; Fig. 4A). Despite the increase in delta coherence (t test, t(3)=3.004, p=0.057; Fig. 4B), there is no other effect on HPC-PFC synchrony. Differently, in the APO 1.5 mg/kg group there were no statistical differences (Fig. 4C,D). Finally, the APO 3 mg/kg dose has the opposite effect of the low dose, inducing an theta prominent state. There

is a gradual increase in the theta/delta ratio over time and an increase in low theta relative power accompanied by a decrease in delta coherence. Effects in relative power occur at both PFC (delta: t test, t(4)=3.363, p=0.028; low theta: t test, t(4)=2.166, p=0.096; Fig. 4E) and HPC (delta: t test, t(4)=2.953, p=0.041; low theta: t test, t(4)=2.357, p=0.077; Fig. 4E). Furthermore, the reduction in delta coherence (t test, t(4)=3.026, p=0.038; Fig. 4F) is accompanied by a non-significant reduction in high theta coherence (t test, t(4)=2.162, p=0.096; Fig. 4F).

APO dose-dependent effects on slow oscillations are also partially seen in low gamma oscillations (Fig. 5). APO 0.75 mg/kg, but not higher doses, increases low gamma coherence (t test, t(3)=4.411, p=0.021; Fig. 5C) without significantly affecting relative power or other measures of synchrony. APO 3 mg/kg, but not lower doses, increases low gamma relative power without affecting synchrony. This increase in relative power occurs in both PFC (Wilcoxon, W=15, p=0.062; Fig 5F) and HPC (Wilcoxon, W=15, p=0.062; Fig. 5G). Interestingly, APO 0.75 mg/kg induces a gradual increase in coherence over time, which does not occur at other doses (Fig. 5A). Finally, another differential effect between APO doses is the change in the PSD slope. While APO 0.75 mg/kg administration produced an increase in the PSD slope, APO 1.5 mg/kg e 3 mg/kg groups showed a decrease in this slope (Fig. 5B,D,F)

These data show that APO administration have opposite effects on oscillations according to the dose used. Low doses produce a delta prominent state, while higher doses increase theta oscillations predominance.

Changes in the dynamics of oscillatory states after DA administration

In order to more selectively investigate the effects of dopaminergic neurotransmission, we administered DA 500 nmol or DA 100 nmol doses. DA 500 nmol group showed an increase in the time proportion of TRANS states (t test, t(12)=2.735, p=0.018; Fig. 6B). In contrast, the 100 nmol DA group exhibited a prevalence of DEA states, with both higher time proportion (t test, t(7)=6.305, p<0.001; Fig. 6A) and higher average time proportion (t test, t(7)=2.392, p=0.048; Fig. 6B) of DEA states. Eesse efeito foi acompanhado da reduction in time proportion of ACT states (t test,

t(7)=3.843, p=0.006; Fig. 6A). These results demonstrate that DA induces a predominance of DEA states at a low dose but less clear changes at a high dose.

Spectral and connectivity changes after DA administration

We observed that both DA doses induce changes in coherence and power, as well as in theta/delta ratio, especially in the initial 20 minutes after injection (Figs. 7A-B and 9A-B). Interestingly, despite the increase in DEA state, DA 100 nmol initially induces a decrease in delta oscillations. Both delta coherence and HPC delta relative power were reduced (HPC delta: t test, t(7)=2.735, p=0.029; delta coherence: t test, t(7)=2.839 p=0.025; Fig. 8A,B). DA 500 nmol produced similar but more robust effects, resulting in delta suppression and theta predominance. Specifically, DA 500 nmol induced a general reduction in delta relative power (PFC: t test, t(12)=3.550, p=0.004; HPC: t test, t(12)=3.846, p=0.002; Fig. 10A) accompanied by a general increase in theta relative power (PFC – low theta: t test, t(12)=3.413, p=0.005; PFC – high theta: t test, t(12)=2.805, p=0.015; HPC – low theta: t test, t(12)=3.969, p=0.001; HPC – high theta: t test, t(12)=2.743, p=0.017; Fig. 10A). Despite the robust effects in theta relative power, DA 500 nmol does not affects low theta coherence but reduces delta coherence (t test, t(12)=3.098, p=0.009; Fig. 10B) and increases high theta coherence (t test, t(12)=2.682, p=0.019; Fig. 10B). The increase in HPC-PFC connectivity promoted by DA 500 nmol also includes an increase in theta PPC and theta DWPLI (PPC – low theta: t test, t(12)=3.212, p=0.007; PPC – high theta: t test, t(12)=3.582, p=0.003; DWPLI – low theta: t test, t(12)=3.238, p=0.007; DWPLI – high theta: t test, t(12)=3.852, p=0.002; Fig. 10B). These results indicate that higher dopamine doses induce increased theta power and synchrony, promoting HPC-PFC connectivity without bias by power or dependence on volume conduction.

Interestingly, both DA doses exhibited a late effect, which peaks around 30 to 40 minutes after injection. While DA 500 nmol produced more robust effects in the initial post-injection period, DA 100 nmol resulted in more expressive effects in the late period. During this late effect, the DA 100 nmol group showed an increase in HPC delta relative power (t test, t(7)=3.535, p=0.009; Fig. 8C) and a decrease in theta relative power in the same region (low theta: t test, t(7)=4.403,p=0.003; high theta: t test, t(7)=2.433, p=0.045; Fig. 8C). There was also an increase in delta coherence (t test,

t(7)=2.153, p=0.068; Fig. 8D) and a reduction in high theta coherence (t test, e agt(7)=2.144, p=0.069; Fig. 8D), but no change in phase synchrony. Notably, most of these effects are opposite to those observed in the initial period after administration of the same dose. This pattern was also observed in the DA 500 nmol group, with no effects on relative power, but it was observed a reduced high theta coherence (Wilcoxon, W=-87, p<0.001; Fig. 10D). This effect contrasts with the increase in high theta phase coherence and synchrony observed in the initial post-injection period. In general, the oscillatory changes in the initial and late period demonstrate that the effects resulting from the administration of DA are manifested not only dose-dependently but also in a time-dependent way.

Absence of effects on the dynamics of oscillatory states after administration of dopamine agonists SKF (D_1) and QUIN (D_2)

To investigate whether the effects observed by DA administration are receptor-specific, we administered the selective D_1 receptor agonist, SKF, and the D_2 receptor agonist, QUIN. We found that both SKF and QUIN agonists, regardless of dose, do not promote changes in the time proportion of oscillatory states (Fig. S1A-D) and therefore do not reproduce the effects exhibited by dopamine on the dynamics of urethane oscillatory states.

Absence of spectral and connectivity changes after SKF administration

We observed that both doses of SKF (1 and 10 μg) did not produce evident changes in spectrograms or in theta/delta ratio relative power (Fig. S2). However, SKF 10 μg produced a trend towards reduced low theta coherence (t test, t(5)=2.352, p=0.065; Fig. S3D), which is the opposite effect of the higher dose of dopamine administration. No other effects on synchrony were observed. The almost total absence of effects may possibly indicate that the selected D_1 agonist doses are insufficient to reproduce a physiological activation of D_1 receptors.

Spectral and connectivity changes after QUIN administration

We found that both doses of QUIN (1 μg and 10 μg) induced visible changes in spectrograms and in theta/delta ratio relative power (Fig. 11). Although there were no effects in the initial post-injection period, QUIN shifts oscillations to a delta prominent

state in the late period. In HPC, QUIN 1 µg resulted in an increase in delta relative power (t test, t(5)=2.966, p=0.031; Fig. 12E) and a low theta relative power reduction (t test, t(5)=3.299, p=0.021; Fig 12E). These effects were accompanied by a reduction in PFC theta relative power (Wilcoxon, W=-21, p=0.031; Fig. 12E) and a reduction in high theta coherence (t test, t(5)=3.169, p=0.024; Fig. 12F). Furthermore, we verified an increase in delta coherence (t test, t(5)=3.960, p=0.010; Fig. 12F), which was also observed after APO 0.75 mg/kg and DA 100 nmol administration, the two lowest doses of the respective drugs. Given that APO operates on D_1 and D_2 receptors, and DA may have more affinity for D_2 receptors than D_1 (Marcellino et al., 2011), D_2 receptor agonism may be especially associated with increased delta activity. Interestingly, the highest dose of QUIN had similar but more robust effects to the lower dose. In both HPC and PFC, QUIN 10 µg resulted in an increase in delta relative power (PFC: t test, t(5)=2.634, p=0.046; HPC: t test, t(5)=2.678, p=0.043; Fig. 12G) and a decrease in low theta relative power (PFC: t test, t(5)=3.035, p=0.028; HPC: t test, t(5)=2.775, p=0.039; Fig. 12G). We also found that a general increase in delta synchrony accompanied these effects. Specifically, there was an increase in delta coherence (t test, t(5)=5.814, p=0.002; Fig. 12H) and delta phase synchrony (PPC – t test, t(5)=3.054, p=0.028; DWPLI – t test, t(5)=3.263, p=0.022; Fig. 12H). Finally, there was an increase in low theta coherence (t test, t(5)=4.166, p=0.008; Fig. 12H). Taken together, these results demonstrate that QUIN activation of dopaminergic D_2 receptors results in late oscillatory and dose-dependent changes, among which the increase in delta power and connectivity stands out.

Drugs	**Power**						**Coherence**				**PPC**			**DWPLI**	
	Delta		Low theta		High theta		Delta	Low theta	High theta	Delta	Low theta	High theta	Delta	Low theta	High theta
	PFC	HPC	PFC	HPC	PFC	HPC	HPC-PFC	HPC-PFC	HPC-PFC	HPC-PFC	HPC-PFC	HPC-PFC	HPC-PFC	HPC-PFC	HPC-PFC
APO 0.75 mg/kg		↗		↘		↓	↗								
APO 1.5 mg/kg															
APO 3 mg/kg	↓	↓	↗	↗			↓		↘						

DA 100 nmol	↗	↓ ↑	↘	↓	↓	↗	↓ ↗		↘							
DA 500 nmol	↓	↓	↑	↑	↑	↑	↓		↑ ↓		↑	↑		↑	↑	
SKF 1 µg																
SKF 10 µg								↘								
QUIN 1 µg		↑		↓	↘		↑	↘ ↘	↓							
QUIN 10 µg	↑	↑	↓	↓	↘		↑	↓		↑			↑			

Table 1. Summary of main oscillatory changes in initial (blue) or late (red) periods after drug injections. Legend: ↑, increase, $p<0.05$; ↓, reduction, $p<0.05$; ↗, increase trend, $p<0.1$; ↘, reduction trend, $p<0.1$.

Discussion

In this study, we investigated the specific effects of selective and non-selective agonism of D_1 and D_2 dopamine receptors and the exogenous DA effects on HPC-PFC oscillatory dynamics. Our results show that DA modulates brain dynamics inducing theta oscillations in HPC-PFC circuits. In a higher dose, DA increases theta relative power, as well as theta phase synchrony and coherence. These oscillatory changes are distinct from the nonspecific agonist apomorphine, which in low dose shifts brain oscillation to a delta prominent state, increasing delta relative power and coherence. In higher dose induces a theta state, reducing delta relative power and coherence and increasing theta relative power. Furthermore, selective agonism of D_1 or D_2 dopamine receptors did not reproduce the effects of DA on the brain, however, D_2 agonism produced a delta prominent state in the late period after injection, increasing delta relative power, as well as delta phase synchrony and coherence.

Effects on oscillatory brain state

Urethane anesthesia produces oscillatory states that spontaneously alternate between activated (ACT) and deactivated (DEA) periods and whose activity patterns are similar to those presented in natural sleep states (Clement et al., 2008). During ACT states, rapid low-amplitude oscillations and an HPC to PFC 4 Hz synchronization predominate. In DEA states, there are high amplitude slow oscillations and a PFC to

HPC 1 Hz synchronization predominance (Lopes-Aguiar et al., 2020). Experimental studies have shown that sleep and wakefulness (Oishi & Lazarus, 2017) and urethane anesthesia are both regulated by D_1- and D_2-like dopaminergic receptors (Monti & Jantos, 2008). Our results reveal that dopamine and nonspecific agonist apomorphine, but not the selective D_1 and D_2 agonists, induce dose-dependent changes in urethane oscillatory states.

We show that nonspecific D_1/D_2 APO agonism has a dose-dependent effect on HPC-PFC oscillatory dynamics. Actually, APO is known to produce biphasic effects on sleep-wake regulation. While a low dose produces sedative effects and increases the slow oscillations (Kropf & Kuschinsky, 1991, Monti & Jantos, 2008; Xu et al., 2011), high doses promote the opposite effect (Monti & Jantos, 2008). Our data confirm this biphasic APO pattern. While a low APO dose induced DEA states predominance, delta activity increase, and theta reduction, a high dose promoted ACT states predominance, delta activity reduction, and theta increase. The intermediate APO dose induced a theta oscillation peak in the PSD without statistical effect, indicating a possible weaker or more variable effect. This biphasic APO effect possibly occurs because low agonist doses act on dopaminergic neurons' autoreceptors, inhibiting these neurons and decreasing DA release, while high doses stimulate postsynaptic receptors, releasing DA directly (Skirboll et al., 1979; Monti & Jantos, 2008). Additionally, low APO doses reduce dopaminergic firing rate (Bunney et al., 1973; Mallet et al., 2008; Assié et al., 2009; Xu et al., 2011), while higher doses can promote neuronal excitability (Yanagihashi et al., 1991).

Our results indicate that higher APO doses possibly induce a hyperdopaminergic state characterized by an increase in HPC and PFC low gamma relative power. It is well established that similar APO doses induce behavioral stereotypy and hyperlocomotion (Geyer et al., 1986). Both gamma band power aberrant changes (Lee et al., 2003) and behavioral stereotypy, in addition to the psychosis symptom, are characteristic of schizophrenia pathology, which according to the dopaminergic hypothesis of schizophrenia, is associated with hyperdopaminergic states. (Meltzer & Stahl, 1976). Interestingly, unlike drugs such as amphetamines, which at high doses reproduce schizophrenia symptoms by increasing the synaptic DA

availability, it is unclear whether hyperdopaminergia generated by high APO doses precisely reproduces the psychosis symptom (Dépatie & Lal, 2000). A possible explanation is that APO acts directly on postsynaptic dopaminergic receptors, showing a higher affinity for D_2 receptors and a lower affinity for D_3 receptors than the DA molecule (Dépatie & Lal, 2000). This would explain why APO partially reproduces schizophrenia symptoms compared to drugs releasing DA into synapses and helps to explain the differences between APO and DA in HPC-PFC oscillatory dynamics shown in our results.

Our results show that DA administration promotes dose- and time-dependent changes in HPC-PFC oscillatory dynamics. In the initial post-injection period, both DA 100 nmol and 500 nmol doses induced theta oscillations and ACT states predominance for at least 10 continuous minutes, but DA 500 nmol effects were more expressive and permanent, showing higher theta synchrony. These results confirm previous studies (Benchenane et al., 2010), indicating active DA participation in HPC-PFC oscillatory states regulation and sleep-wake systems (Oishi & Lazarus, 2017; Monti & Jantos, 2008). Interestingly, it was shown that acute dopamine depletion suppresses REM sleep and that hyperdopaminergia generated by D_2 agonist administration was necessary, but possibly not sufficient by itself, to restore REM-like oscillations (Dzirasa et al., 2006). This result indicates that the regulation of oscillatory states may depend on the dopamine interaction with other neurotransmitter systems, such as the cholinergic system (Lester et al., 2010; Monti & Jantos, 2008). Indeed, cholinergic agonists can produce ACT states, while cholinergic antagonists produce prolonged DEA states (Clement et al., 2008, Schall & Dickson, 2009). These results suggest that dopaminergic and cholinergic systems may interact in maintaining urethane states and the sleep-wake system (Dzirasa et al., 2006, Monti & Jantos, 2008).

In the late post-DA injection period, changes in oscillatory dynamics are precisely opposite to those in the initial period. DA 100 nmol dose induced theta oscillations reduction and delta oscillations predominance. DA 500 nmol dose did not produce the same effect but induced a reduction in high theta coherence. One explanation for this late phenomenon of oscillatory dynamics changing involves an alternative cell signaling cascade induced only by D_2 receptors (Dimpfel, 2008).

Although D_1 and D_2 receptor's cellular signaling pathway is traditionally known to involve G-proteins and cAMP-PKS pathways, DA can act via cAMP-independent mechanisms, such as β-arrestin proteins, which allow the desensitization of G-protein-coupled receptors (Beaulieu et al., 2005). The effect generated is an increase in delta activity beginning approximately 30 minutes after D_2 dopamine receptor agonists or exogenous DA administration (Dimpfel, 2008). This evidence explains the late effect observed in our results.

HPC-PFC oscillatory synchrony

One of our study's main results was that DA could induce HPC-PFC theta synchrony. Consistent with our result, Benchenane et al. (2010) showed that DA infused into the PFC of anesthetized rats could induce HPC-PFC theta coherence and reorganize PFC neurons firing rate into theta. However, this result was demonstrated with a low sample of animals, requiring further experimental confirmation with an adequate number of animals. Furthermore, to assess HPC-PFC synchrony, Benchenane et al. (2010) used only spectral coherence, which is highly dependent on spectral power and, therefore, possibly biased. Notably, Benchenane et al. (2010) note that despite the coherence increase, there is no power change in both HPC and PFC, indicating that DA increased phase synchrony. Using synchrony measures independent of power we showed that the increase in HPC-PFC theta phase synchrony occurs robustly in many animals following DA administration. Interestingly, Xu et al. (2016) showed in anesthetized rats that a reduction in HPC-PFC theta phase synchrony and theta power could be induced after D_1 receptor antagonist administration. In contrast, D_1 receptor agonist systemic administration increased theta coherence in pharmacological animal models of schizophrenia but not in control animals (Perreault et al., 2017). Despite these effects observed in literature, our results do not indicate D_1 receptor agonism participation in HPC-PFC synchrony, indicating that the dose used was insufficient to mimic DA activity. Indeed, the doses used in the studies described (Xu et al., 2016; Perreault et al., 2017) were at least 10 times higher than the highest dose used in our study. In another study, a reduction in HPC-PFC theta phase synchrony was observed in freely-moving animals after D_2 receptor agonist or antagonist infusion (Gener et al., 2019). Furthermore, D_2 receptor agonism, but not

antagonism, increased delta phase synchrony (Gener et al., 2019). These effects are similar to the late effect of D_2 agonism observed in our study. In fact, the results presented by Gener et al. (2019) refer to the period between 25 and 35 minutes after D_2 agonist or antagonist administration, indicating that the observed effect may be a late phenomenon resulting from the alternative mechanism of D_2 receptors functioning described previously. Finally, despite this set of studies showing dopaminergic participation in HPC-PFC coherence and phase synchrony, it is not possible to state whether the effects being measured in these studies would not be a reflection of electrical currents conducted by volume from HPC to cortex (Sirota et al., 2008). Our results using DWPLI (Vinck et al., 2011), a phase synchrony measure unbiased by volume conduction, indicate that the HPC-PFC phase synchrony observed is independent of volume conduction.

Oscillatory synchrony is proposed as the most efficient mechanism for neuronal activity temporal coordination (Buzsáki & Draguhn, 2004) and is essential for information transfer between distant brain regions (Varela et al., 2001; Harris & Gordon, 2015), being the main functional connectivity measure between brain regions (Gordon, 2011). It is proposed that synchrony between neuronal groups, measured as coherence between oscillations, establishes the necessary conditions for selective and effective information transfer between brain regions (Fries, 2005; 2015). In contrast, it is also proposed that this synchrony derives from the structural connectivity between neuronal groups and would therefore be a consequence, not the cause, of the functional connectivity (Schneider et al., 2021). However, both proposals for synchrony as a cause or consequence of functional connectivity are consistent with the fact that synchrony is not a fixed process but rather dynamic and modulable. In this sense, our results provide evidence that dynamic control of synchrony between distant regions may directly involve dopaminergic participation. Indeed, it has been shown in rodents that HPC-PFC theta synchrony increase can occur during new environments exploration (Siapas et al., 2005; Sirota et al., 2008; Dzirasa et al., 2009), exposure to anxiogenic stimuli (Adhikari et al., 2010) and performing cognitive tasks involving decision making and working memory (Jones & Wilson, 2005; Sigurdsson et al., 2010; Benchenane et al., 2010; Hyman et al., 2010; O'Neill et al., 2013). In cognitive tasks,

synchrony has been shown to change as a function of performance (Hyman et al., 2010; Benchenane et al., 2010; Sigurdsson et al., 2010, O'Neill et al., 2013) and peak at decision-making moments after learning the task rules (Benchenane et al., 2010). This HPC-PFC theta synchrony at decision-making choice is reproduced by infusing physiological amounts of exogenous DA into PFC (Benchenane et al., 2010). Notably, under conditions of genetic hyperdopaminergia, impairment in spatial cognitive performance is observed (Dzirasa et al., 2009; Duvarci et al., 2018). Taken together, these studies suggest that HPC-PFC theta synchrony is dynamically adjusted as a function of cognitive demand, and this adjustment may be dependent on dopaminergic action. Consistent with this claim, our results indicate that DA induces an increase in HPC-PFC theta synchrony in a dose-dependent manner, suggesting that DA can promote this dynamic adjustment of synchrony.

One of our study's main limitations is that our results were observed in anesthetized animals. It is known that urethane anesthesia has well-defined oscillatory states, and oscillatory brain patterns in anesthetized animals differ extensively from those observed in awake animals. Thus, additional experiments with freely-moving animals are necessary to generalize the results observed in this study. Furthermore, future studies should address how the precise spatiotemporal control of dopaminergic neurons in the ventral tegmental area, the main source of mesocortical dopamine, modulates the HPC-PFC oscillatory dynamics; how different patterns of dopaminergic release differentially affect HPC-PFC connectivity; and whether dopamine projected from different regions has similar regulatory effects.

Conclusion

Our study provides evidence that HPC-PFC oscillatory states under urethane anesthesia are dose- and time-dependently modulated by dopamine, as well as by the nonspecific apomorphine agonism and the specific D_2 receptor agonism. We also showed that dopamine modulates brain dynamics inducing theta oscillation and theta synchrony in HPC-PFC circuits. Our experimental evidence contributes to a better understanding of the dopaminergic role in oscillatory dynamics coordination and the consequent facilitation of HPC-PFC interaction.

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Figures and Legends

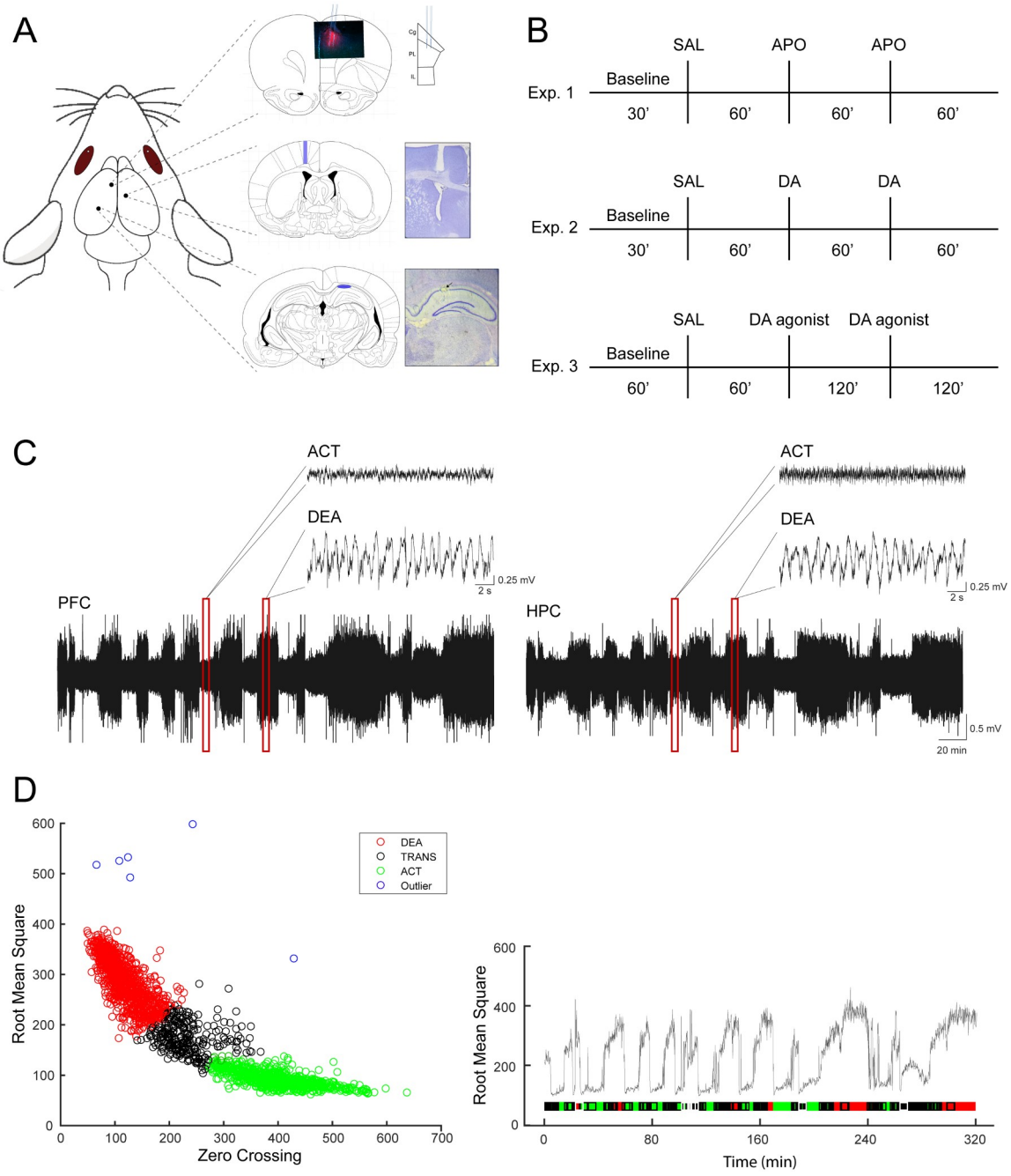

Figure 1. Experimental procedures and classification of oscillatory states under urethane anesthesia. (**A**). Histological sections showing the positioning of the cannula for i.c.v. drug injection e of the electrodes and the silicon probe for recording neural activity. (**B**) Experimental design. (**C**) Representative 320 min recording of raw LFP (bottom) and magnification of 20-second segments showing the spontaneous oscillatory pattern of ACT and DEA states in PFC and HPC (top). (**D**) Classification of oscillatory states under urethane anesthesia. Initially, the states were clustered in an unsupervised manner into three groups by the k-means algorithm. Then, manual adjustments were made to refine the classification. Grouping of 10-second epochs into three categories based on root mean square (RMS) and zero crossings. Epochs with high deviation from the cluster's mean were considered outliers

and removed from the analyses. Comparison of each epoch RMS value with its respective classification.

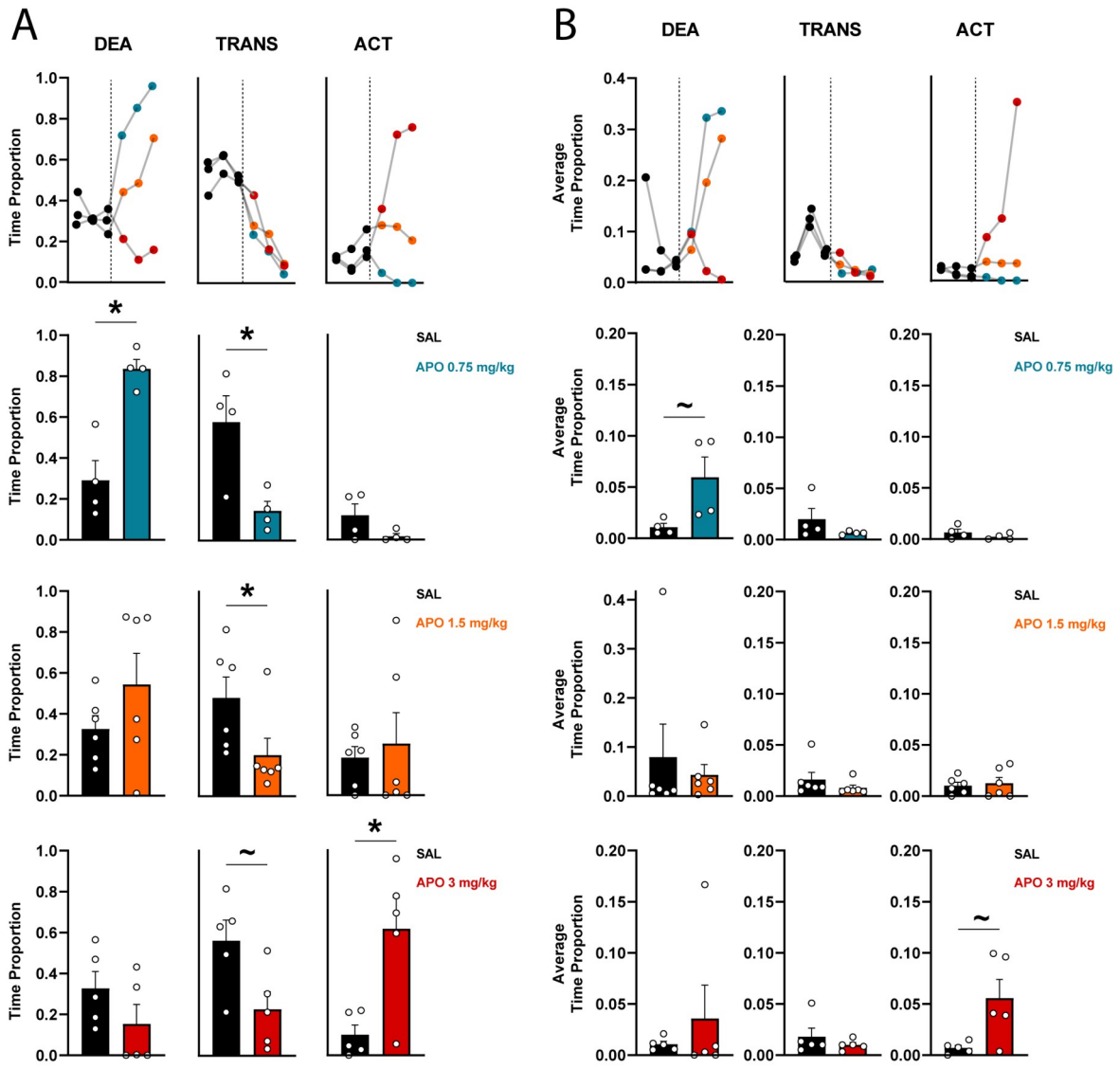

Figure 2. Apomorphine exhibits a dose-dependent effect on the time proportion of oscillatory states. (**A-B**), Line graphs represent the time proportion of states over time, where each point corresponds to an 18-minute block. The dotted vertical line represents the drug injection. The bar graphs correspond to the mean of the blocks of each treatment. (**A**) The proportion of time is obtained by summing the total time during which the respective state occurs. We observed that all doses induce a reduction in the time proportion of TRANS states, which indicates expressive oscillatory shifting to DEA or ACT states. Furthermore, while the 0.75 mg/kg dose induced a significant increase in time proportion of DEA states, the 3 mg/kg dose induced a significant increase in time proportion of ACT states. (**B**) The average time proportion is obtained by averaging the total time during which the respective state occurs. This measure indicates whether a change in the duration of a state is consistent across occurrences of the respective state. We observed that the 0.75 mg/kg dose increases the average time proportion in DEA states, while the 3 mg/kg dose increases in ACT states. Data presented as mean ± SEM. ~p<0.1, *p<0.05.

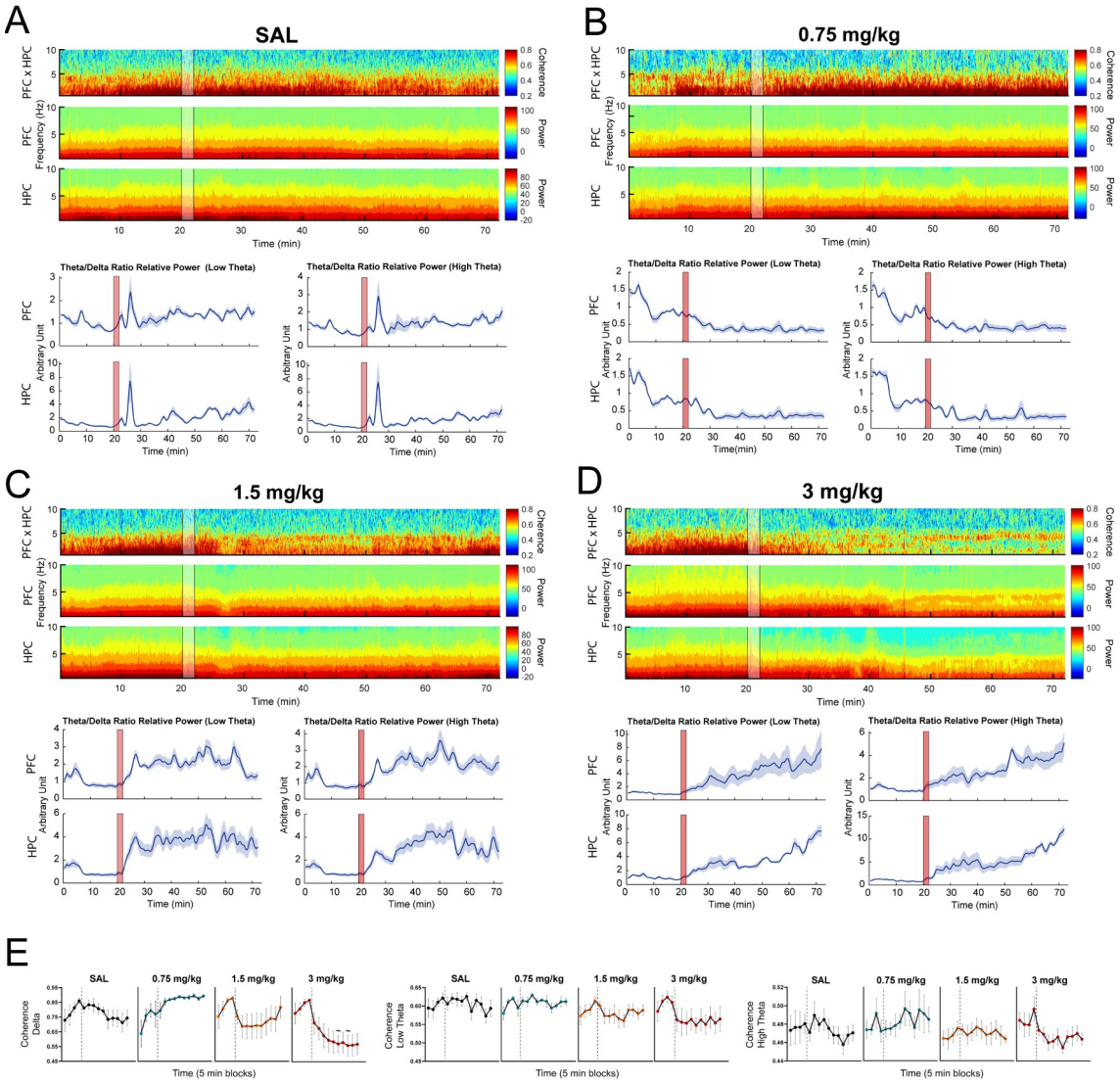

Figure 3. Effects of Apomorphine administration on HPC-PFC dynamics (**A-D**) HPC-PFC coherence and power spectrograms, respectively, for saline injection and three doses of apomorphine. Below the spectrograms, graphs display the relative power of the theta/delta ratio considering two different frequency ranges in the theta band. Theta/delta ratio data are normalized by baseline. Vertical rectangles on spectrograms and theta/delta ratio plots represent the injection period (2 minutes duration). We observed a dose-dependent effect of apomorphine on theta/delta ratio. The 0.75 mg/kg dose reduces the theta/delta ratio (**B**), while 1.5 mg/kg and 3 mg/kg doses increase (**C-D**). (**E**) HPC-PFC coherence over time quantified in 5-minutes blocks for each frequency band. The first four points of the line graphs correspond to the baseline (total period of 20 minutes), and the remaining points correspond to the post-injection period (total period of 54 minutes). Post-injection blocks were compared with the mean of baseline blocks. Data presented as mean ± SEM. ~p<0.1.

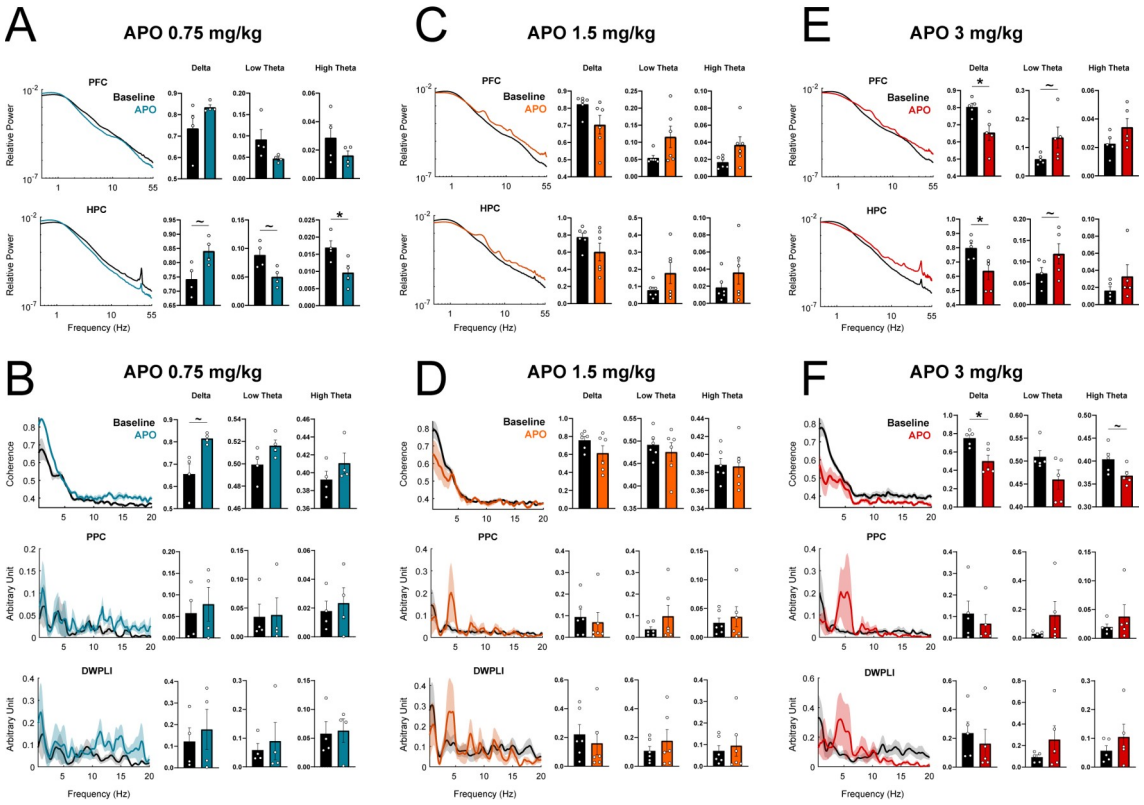

Figure 4. Apomorphine exhibits a dose-dependent effect on HPC-PFC connectivity. Statistical comparisons between the 30-40 minutes period mean after apomorphine injection and the respective injection averaged baseline. (**A-C**) PFC and HPC averaged PSDs. (**D-F**) HPC-PFC synchrony is represented by measures of coherence (top), pairwise phase consistency (PPC, middle), and debiased weighted phase lag index (DWPLI, bottom). Apomorphine 0.75 mg/kg dose increases relative power (HPC) and coherence (HPC-PFC) in delta (**A, D**) and decreases relative power (HPC) in theta frequencies (**A**). In contrast, the 3 mg/kg dose decreases relative power in delta and increases in high theta in both regions (**C**), as well as reduces HPC-PFC coherence in delta and high theta (**F**). The 1.5 mg/kg dose increases theta oscillations in PSDs (**B**), and similarly to the 3mg/kg dose, it shows PPC and DWPLI peaks in theta frequencies (**E, F**), but there are no statistical differences. Data presented as mean ± SEM. ~p<0.1, *p<0.05.

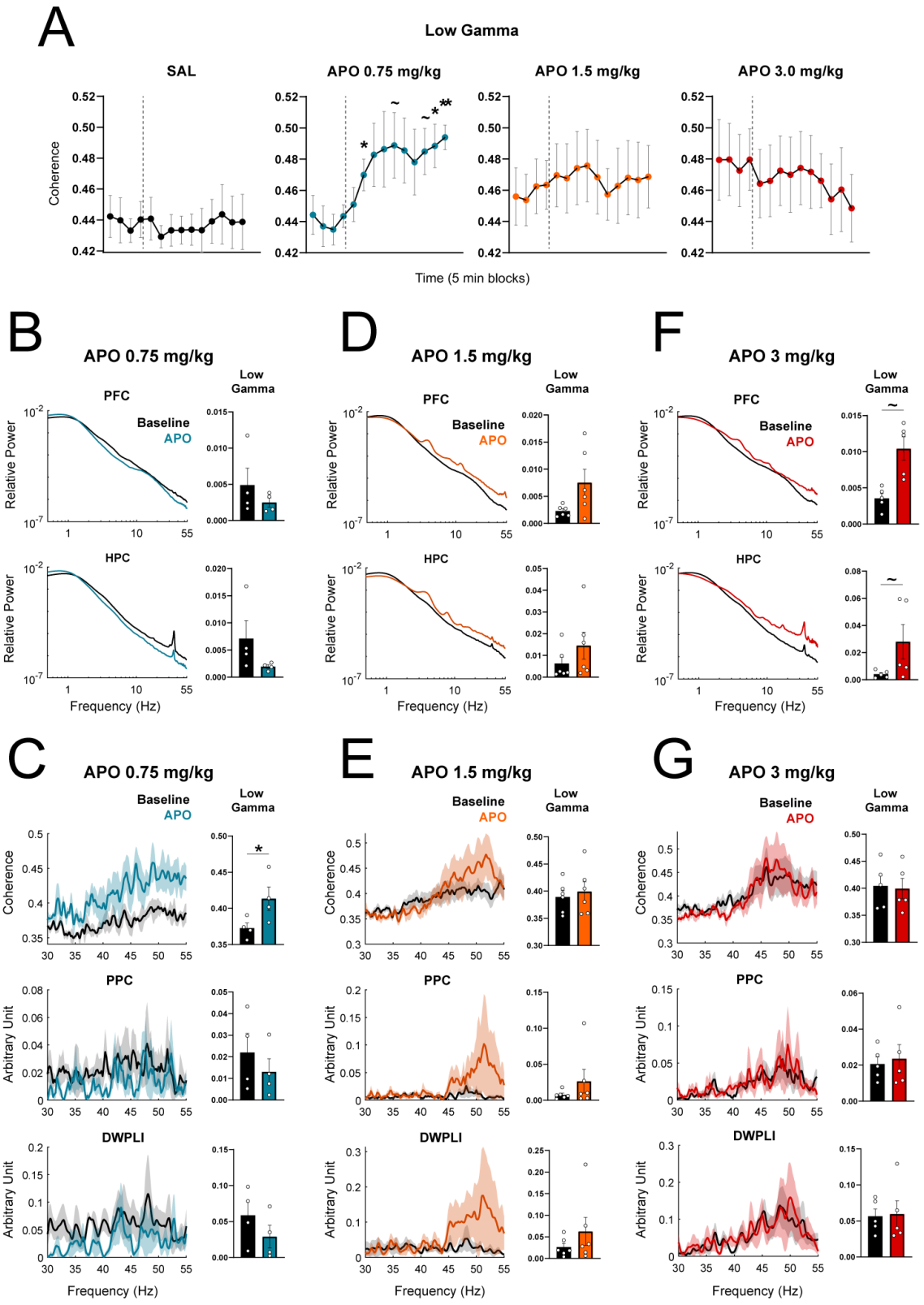

Figure 5. Apomorphine exhibits a dose-dependent effect on HPC-PFC gamma connectivity. Statistical comparisons between the 30-40 minutes period mean after apomorphine injection and the respective injection averaged baseline at 30-55Hz gamma band frequencies. (**A**) HPC-PFC low gamma coherence over time quantified in 5-minute blocks. A continuous increase in coherence is noted over time after the 0.75 mg/kg APO dose injection, which is not observed at the other doses administered. (**B-D**) PFC and HPC averaged PSDs. (**E-G**) HPC-PFC synchrony is

represented by measures of coherence (top), pairwise phase consistency (PPC, middle), and debiased weighted phase lag index (DWPLI, bottom). Data presented as mean ± SEM. ~p<0.1, *p<0.05. The observed effects were an increase in HPC-PFC coherence with no change in relative power after 0.75 mg/kg APO dose injection (**B, E**) and an increase in relative power after APO 3 mg/kg dose injection with no change in HPC-PFC synchrony (**D, G**). No statistical effect was observed after APO 1.5 mg/kg injection (**C, F**).

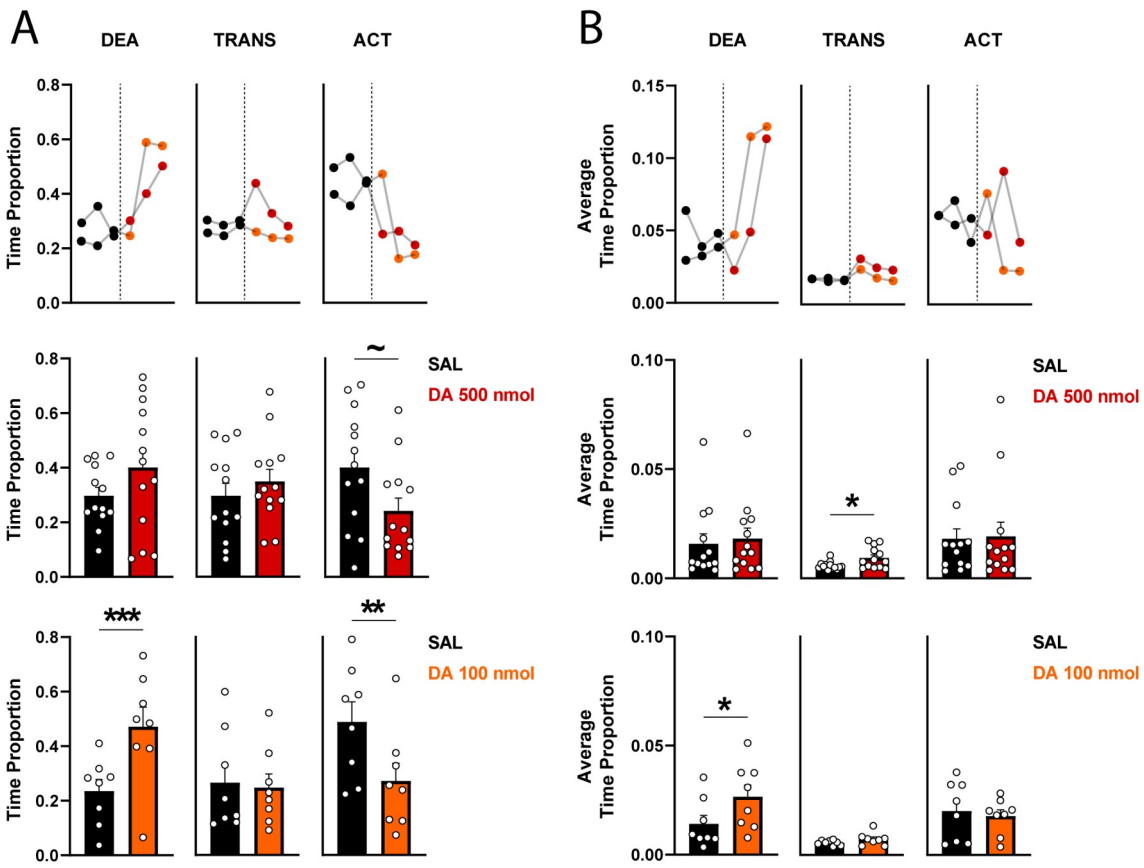

Figure 6. Dopamine affects the duration of oscillatory states in a dose-dependent manner. (**A-B**) Line graphs displaying time proportion (left-top) or average time proportion (right-top) of states in saline or dopamine injections (100 nmol and 500 nmol doses). The bar graphs correspond to the mean of the blocks of each treatment. We observed that DA 100 nmol induces the prevalence of DEA states. (A) DA 100 nmol increases the time proportion in DEA states while it decreases in ACT states. (B) DA 100 nmol also reduces the average time proportion in ACT states, while DA 500 nmol increases in TRANS states.. Data presented as mean ± SEM. ~p<0.1, *p<0.05, **p<0.01, ***p<0.001.

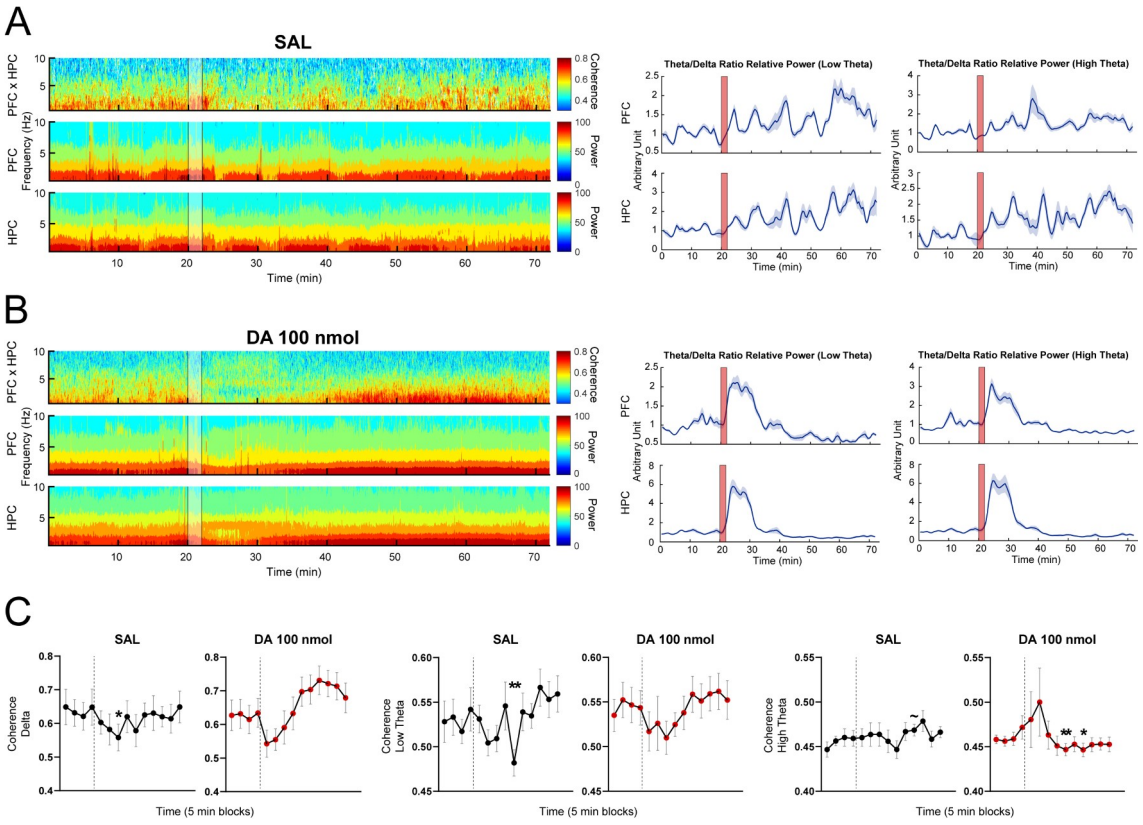

Figure 7. Effects of 100 nmol Dopamine administration on HPC-PFC dynamics. (**A-B**) HPC-PFC coherence and power spectrograms, respectively, for saline injection and dopamine 100 nmol dose. Below the spectrograms, graphs display the relative power of the theta/delta ratio considering two different frequency ranges in the theta band. Theta/delta ratio data are normalized by baseline. Vertical rectangles on spectrograms and theta/delta ratio plots represent the injection period (2 minutes duration). (**B**) DA 100 nmol increases HPC-PFC theta coherence and relative power of theta/delta ratio for at least 10 minutes after injection. The theta/delta ratio returns to baseline levels over the next 40 minutes, indicating delta power predominance and suggesting a reduction in state switching. Note that after saline injection (**A**), the line on the theta/delta ratio graph has many peaks and valleys, reflecting changes in power generated by spontaneous switching between oscillatory states of anesthesia. (**C**) HPC-PFC coherence over time was quantified in 5-minutes blocks for each frequency band. Data presented as mean ± SEM. ~p<0.1, *p<0.05, **p<0.01.

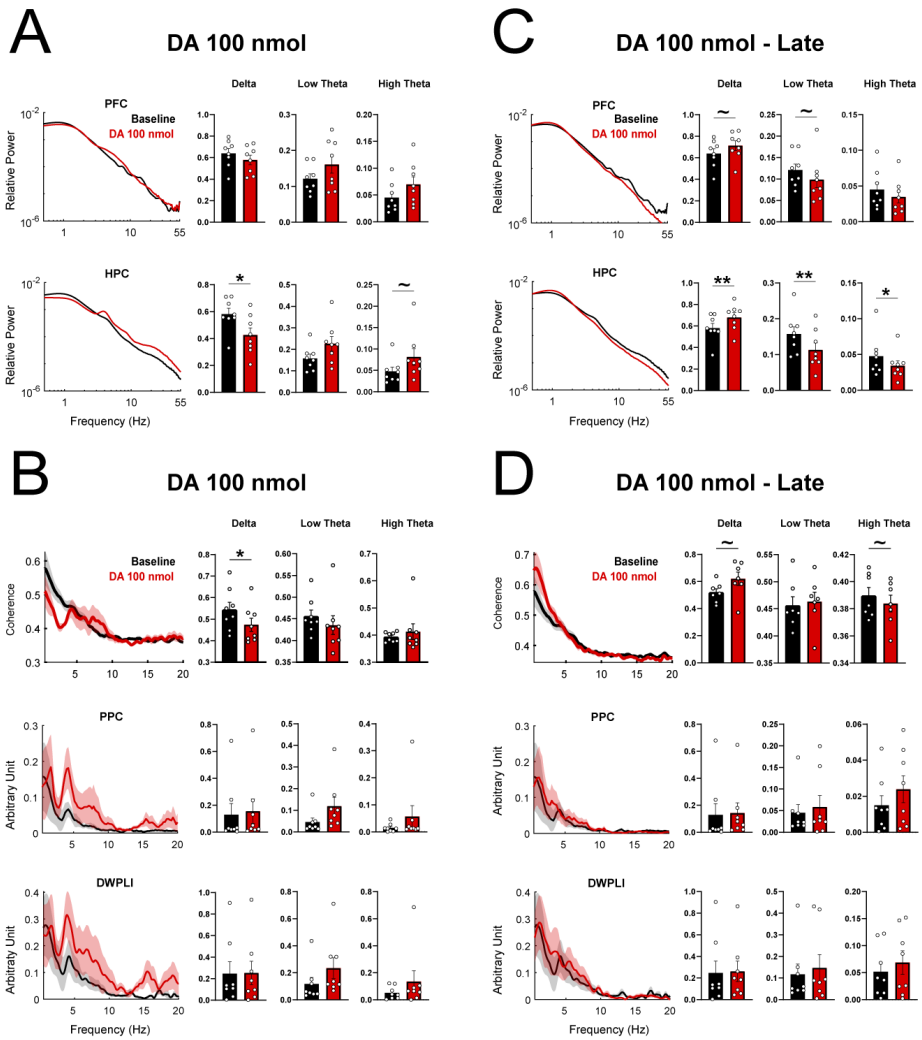

Figure 8. Dopamine 100 nmol changes HPC-PFC connectivity. Statistical comparisons between averaged periods after injection (**A**, **C**, initial period, 2-12 minutes after injection; **B**, **D**, late period, 30-40 minutes after injection) and the respective injection averaged baseline. (**A-B**) PFC and HPC averaged PSDs. (**C-D**) HPC-PFC synchrony is represented by measures of coherence (top), pairwise phase consistency (PPC, middle), and debiased weighted phase lag index (DWPLI, bottom). (**A, C**) In the initial period, DA 100 nmol decreases delta relative power (HPC) and coherence (HPC-PFC), and increases high theta relative power (HPC). (**B, D**) In the late period, DA 100 nmol increases delta relative power and coherence (HPC-PFC), and decreases low theta (HPC and PFC) and high theta (HPC) relative power. Data presented as mean ± SEM. ~p<0.1, *p<0.05.

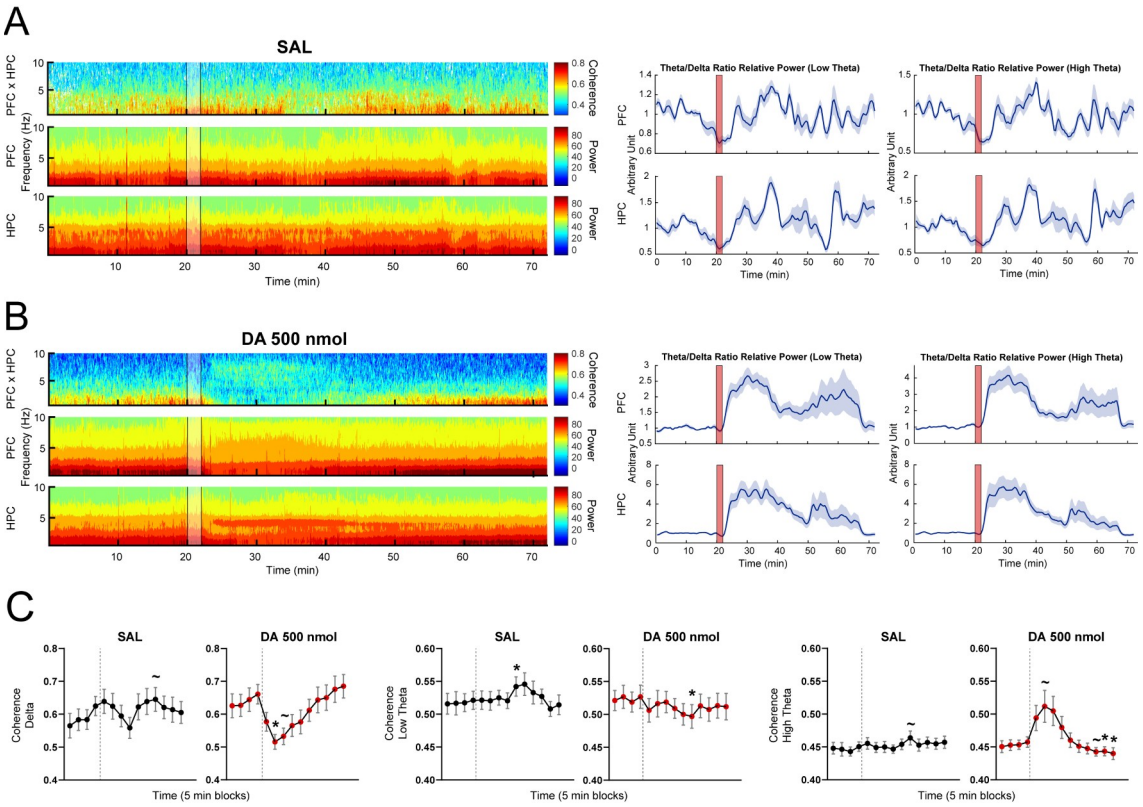

Figure 9. Effects of 500 nmol Dopamine administration on HPC-PFC dynamics. (**A-B**) HPC-PFC coherence and power spectrograms, respectively, for saline injection and dopamine 500 nmol dose. Below the spectrograms, graphs display the relative power of the theta/delta ratio considering two different frequency ranges in the theta band. Theta/delta ratio data are normalized by baseline. Vertical rectangles on spectrograms and theta/delta ratio plots represent the injection period (2 minutes duration). (**B**) DA 500 nmol increases coherence in theta frequencies and relative power of theta/delta ratio for approximately 20 minutes after injection. The theta/delta ratio does not return to baseline levels for the next 30 minutes, indicating a prolonged effect of DA gradually dissipating over time. (**C**) HPC-PFC spectral coherence over time was quantified in 5-minutes blocks for each frequency band. Data presented as mean ± SEM. ~p<0.1, *p<0.05.

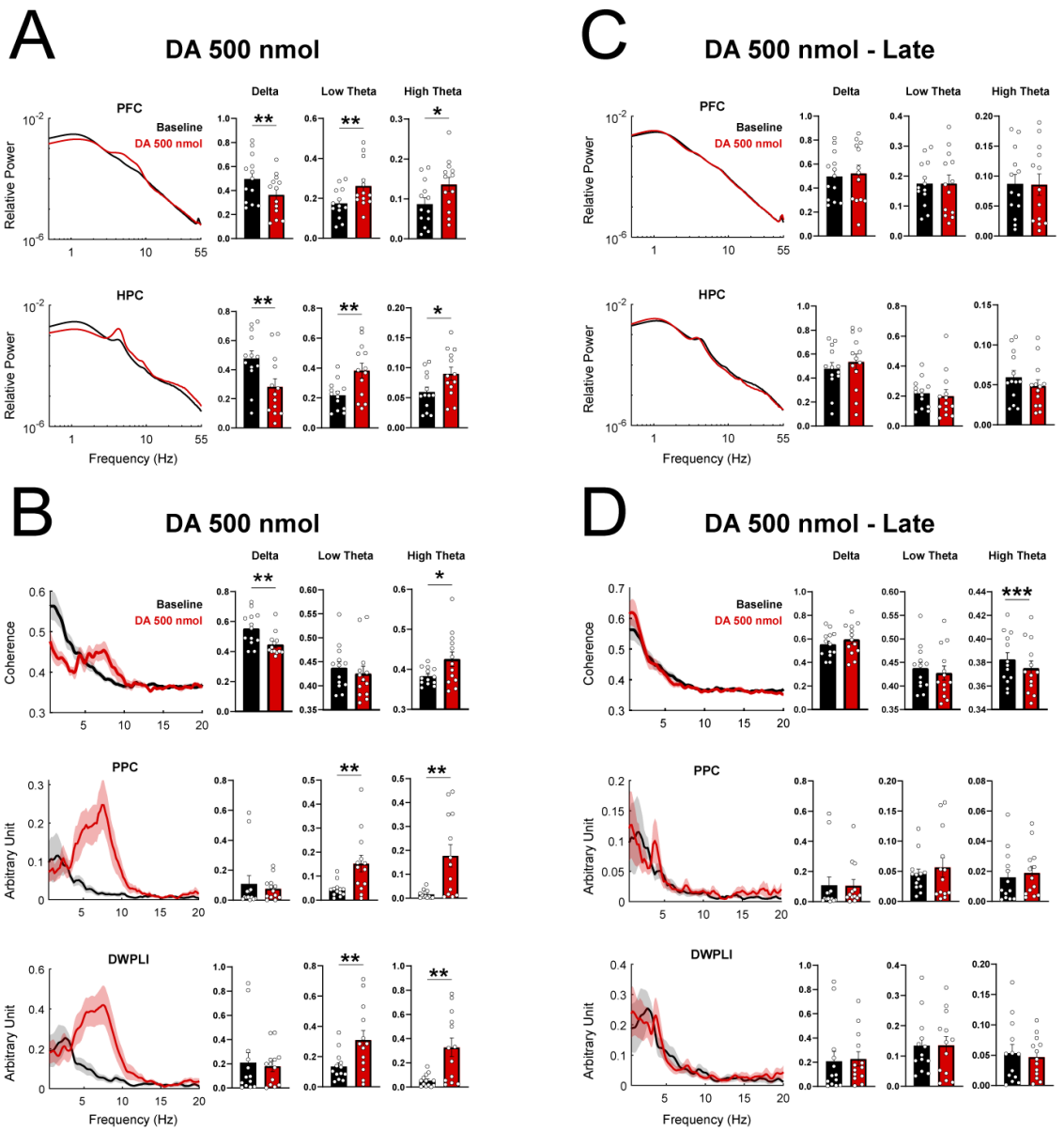

Figure 10. Dopamine 500 nmol changes HPC-PFC connectivity. Statistical comparisons between averaged periods after injection (**A**, **C**, initial period, 2-12 minutes after injection; **B**, **D**, late period, 30-40 minutes after injection) and the respective injection averaged baseline. (**A-B**) PFC and HPC averaged PSDs. (**C-D**) HPC-PFC synchrony is represented by measures of coherence (top), pairwise phase consistency (PPC, middle), and debiased weighted phase lag index (DWPLI, bottom). (**A, C**) In the initial period, DA 500 nmol induces a general increase in relative power and synchrony (HPC-PFC) in theta frequencies, except for low theta coherence (HPC-PFC). Note also the reduction in delta relative power and coherence (HPC-PFC). (**B, D**) In the late period, DA 500 nmol reduces high theta coherence (HPC-PFC) but does not change other measures. Data presented as mean ± SEM. *p<0.05, **p<0.01, ***p<0.005.

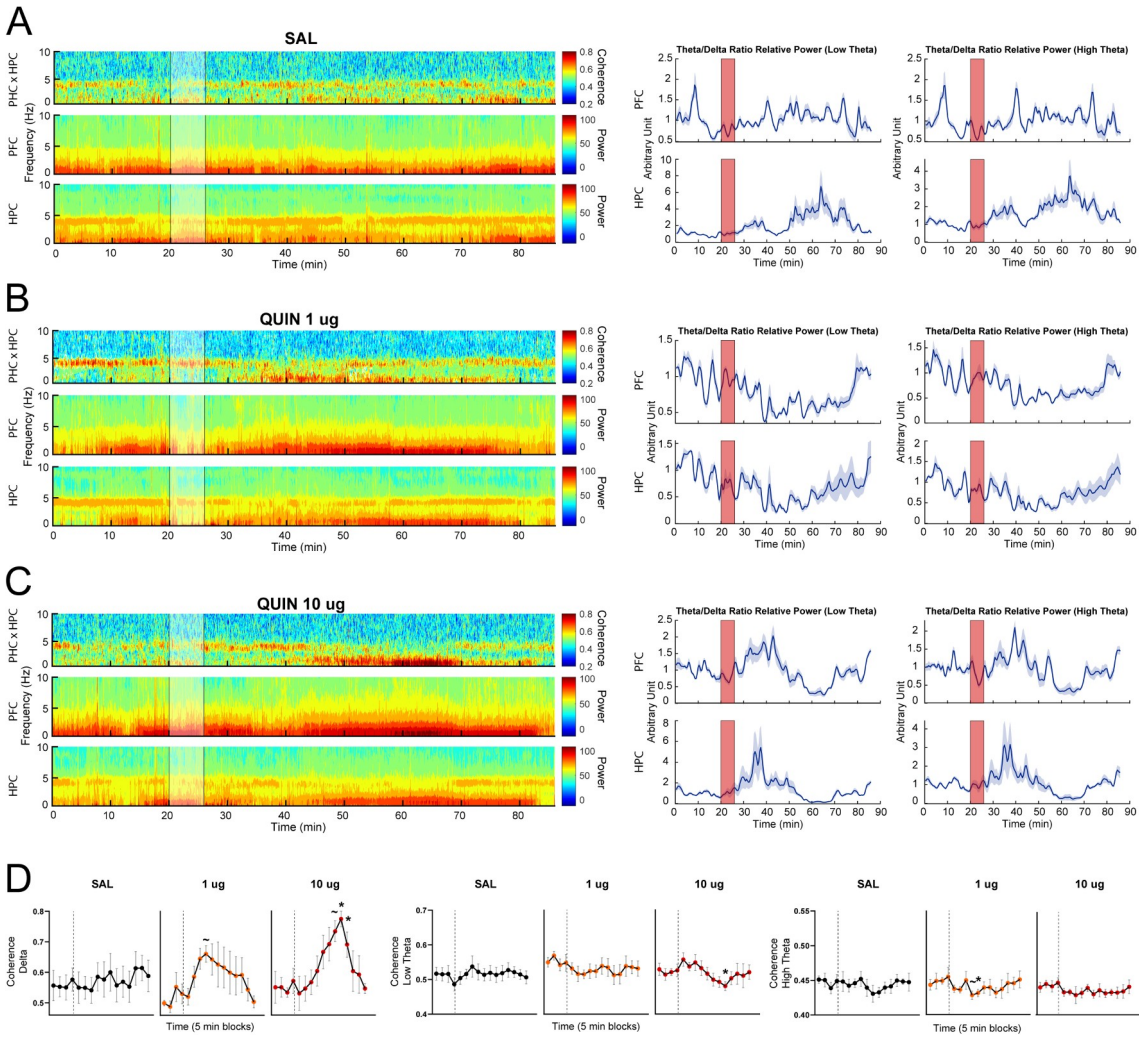

Figure 11. Quinpirole effects on HPC-PFC dynamics. (**A-C**) HPC-PFC coherence and power spectrograms, respectively, for saline injection and QUIN doses (1 µg and 10 µg). Below the spectrograms, the graphs display the relative power of the theta/delta ratio considering two different frequency ranges in the theta band. Theta/delta ratio data are normalized by baseline. Vertical rectangles on spectrograms and theta/delta ratio plots represent the injection period (6 minutes duration). (**D**) HPC-PFC spectral coherence over time was quantified in 5-minutes blocks for each frequency band. (**B, D**) QUIN 1 µg produces no significant changes in the relative power of the theta/delta ratio relative to saline injection but increases coherence peaking 20 minutes after injection. (**C, D**) QUIN 10 µg induces a transient increase in the relative power of the theta/delta ratio in the first 20 minutes and a progressive increase in delta coherence, whose peak occurs between 35 and 45 minutes after injection. Data presented as mean ± SEM. ~p<0.1, *p<0.05.

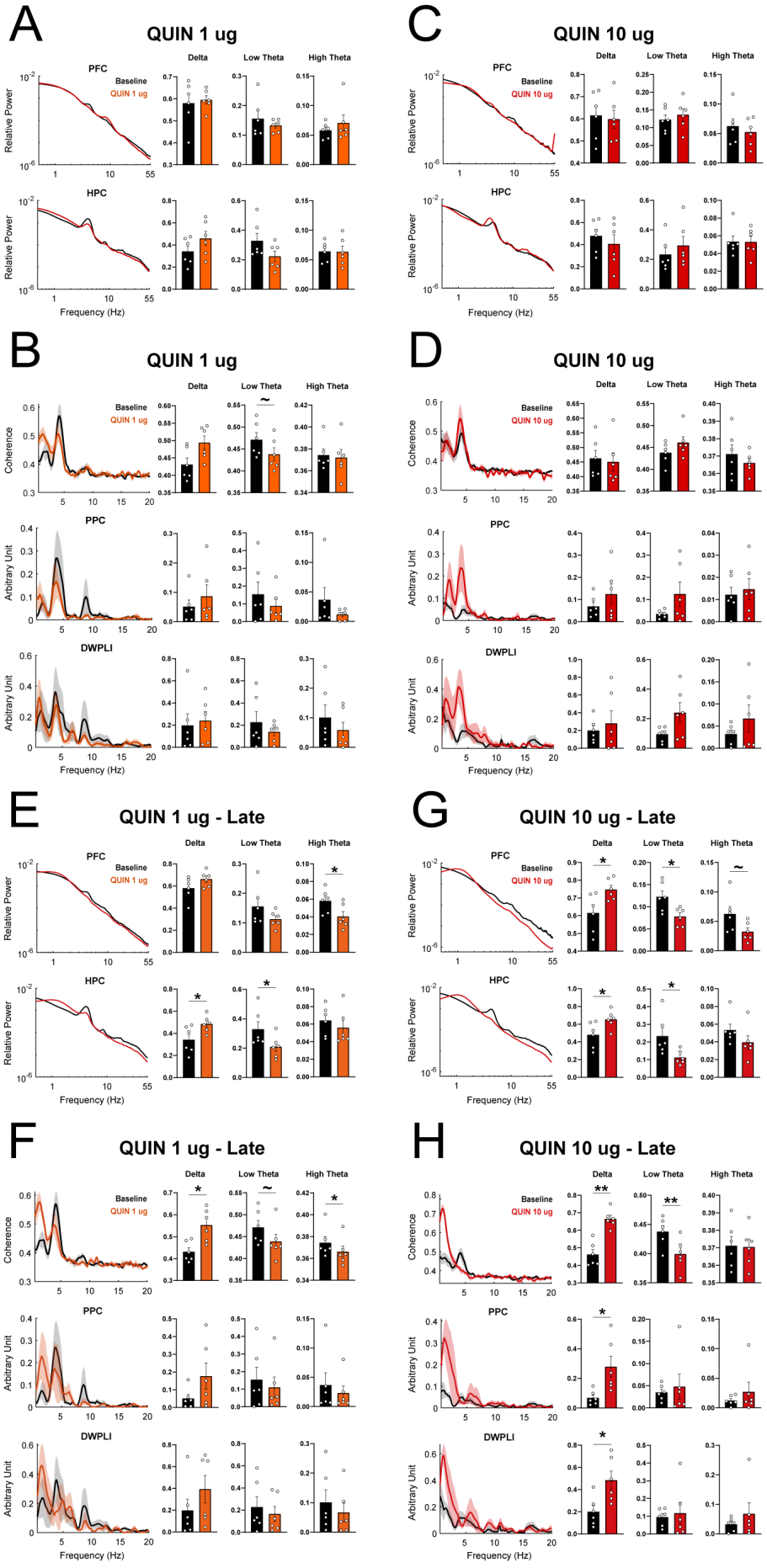
A
QUIN 1 ug
C
QUIN 10 ug
B
QUIN 1 ug
D
QUIN 10 ug
E
QUIN 1 ug - Late
G
QUIN 10 ug - Late
F
QUIN 1 ug - Late
H
QUIN 10 ug - Late
PFC
HPC
PPC
DWPLI
Baseline
QUIN 1 ug
QUIN 10 ug
Delta
Low Theta
High Theta
Relative Power
Coherence
Arbitrary Unit
Frequency (Hz)

Figure 12. Quinpirole changes HPC-PFC connectivity. Statistical comparisons between averaged periods after injection (**A-D**, initial period, 2-12 minutes after injection; E-H, late period, 30-40 minutes after injection) and the respective injection averaged baseline. (**A, B, E, F**) PFC and HPC averaged PSDs. (**C, D, G, H**) HPC-PFC synchrony is represented by measures of coherence (top), pairwise phase consistency (PPC, middle), and debiased weighted phase delay index (DWPLI, bottom). (**A, C**) In the initial period, QUIN 1 μg decreases HPC-PFC low theta coherence but does not change the other measures. (**B, D**). QUIN 10 μg did not significantly affect HPC-PFC power and synchrony. (**E-H**) The main effects of QUIN occur in the late period. (**E, F**) Both doses induce a late increase in relative power in delta (QUIN 1 μg, HPC; QUIN 10 μg, HPC and PFC) and a decrease in theta frequencies (QUIN 1 μg, theta 6-10Hz in PFC, theta 3-6 Hz in HPC; QUIN 10 μg, theta 3-10 Hz in PFC, theta 3-6 Hz in HPC). (**G, H**) There is also an increase in delta synchrony (QUIN 1 μg, coherence; QUIN 10 μg, coherence, PPC, and DWPLI) and a reduction in theta synchrony (QUIN 1 μg, coherence, theta 3- 10 Hz; QUIN 10 μg, coherence, theta 3-6 Hz). Data presented as mean ± SEM. ~$p<0.1$, *$p<0.05$.

Supplementary Figures and Legends

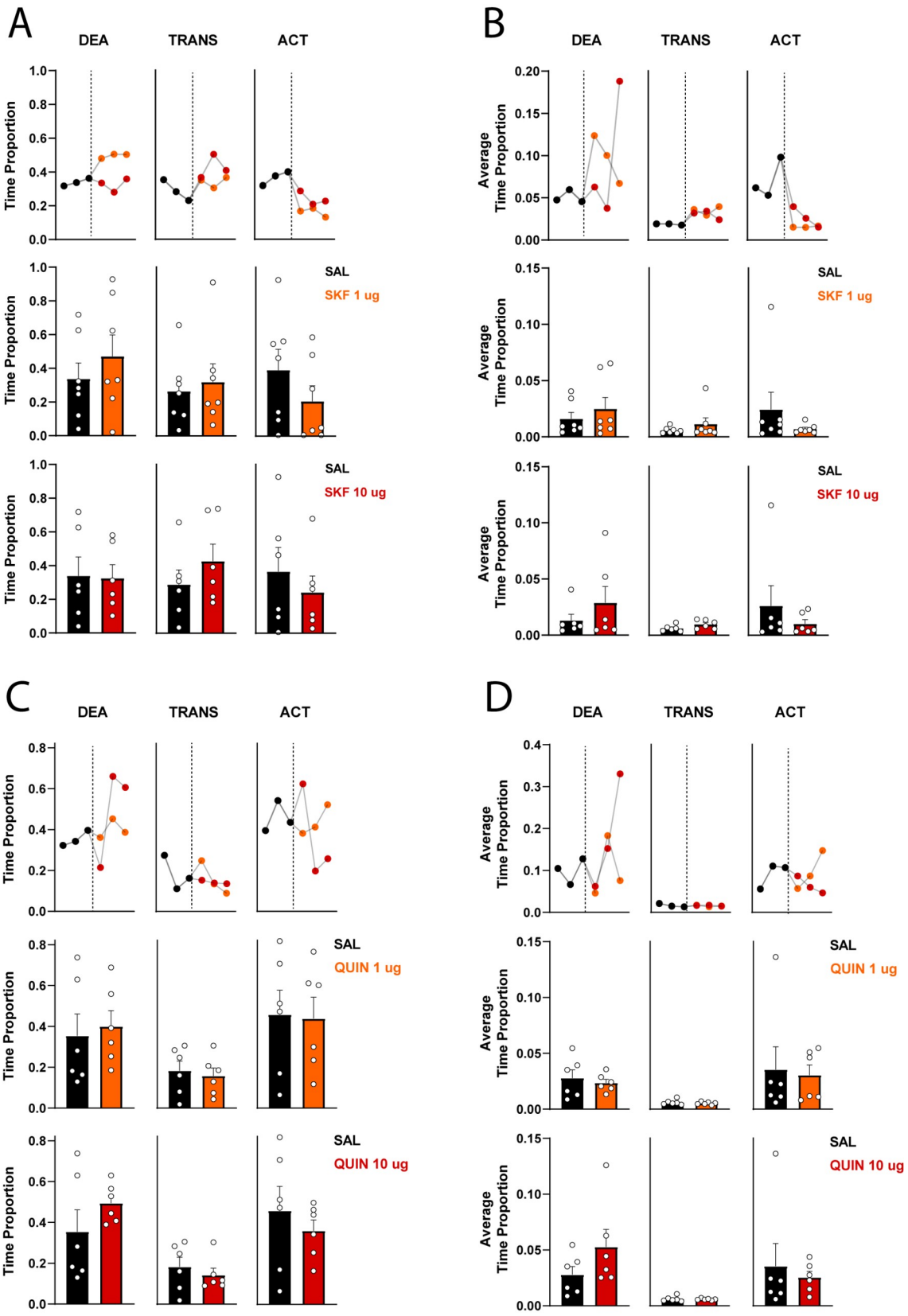

Figure S1. D_1 (SKF) and D_2 (Quinpirole) dopamine agonists do not affect the time proportion of oscillatory states. (**A-D**) Line graphs displaying the time proportion (left-top) or average time proportion (right-top) of states in saline, SKF (1 µg and 10 µg), or QUIN (1 µg and 10 µg) injections. The bar graphs correspond to the mean of the blocks of each treatment. Regardless of the dose, both agonists do not produce significant changes in the time proportion of states. However, differences are visually noted between blocks over time, indicating that the effects of SKF and QUIN doses are not estimated by the average but are noticeable when looking at the blocks individually. Data presented as mean ± SEM.

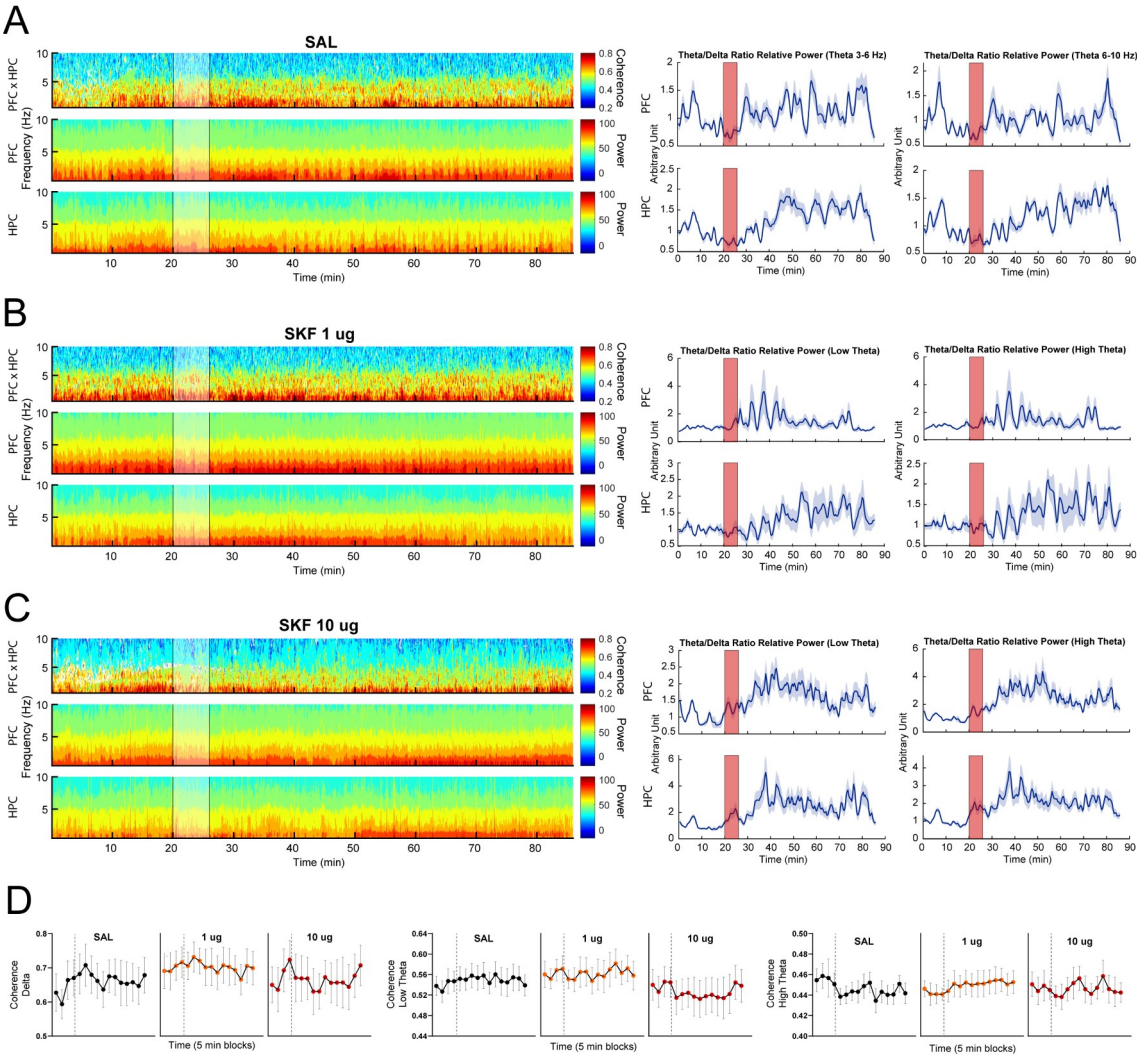

Figure S2. SKF does not affect HPC-PFC dynamics. (**A-C**) HPC-PFC coherence and power spectrograms, respectively, for saline injection and SKF doses (1 µg and 10 µg). Below the spectrograms, the graphs display the relative power of the theta/delta ratio considering two different frequency ranges in the theta band. Theta/delta ratio data are normalized by baseline and presented as mean ± SEM. Vertical rectangles on spectrograms and theta/delta ratio plots represent the injection period (6 minutes duration). (**D**) HPC-PFC spectral coherence over time was quantified in 5-minutes blocks for each frequency band. (**A-D**) Both doses of SKF produced no significant changes in spectral coherence and relative power of theta/delta ratio relative to saline injection. Data presented as mean ± SEM.

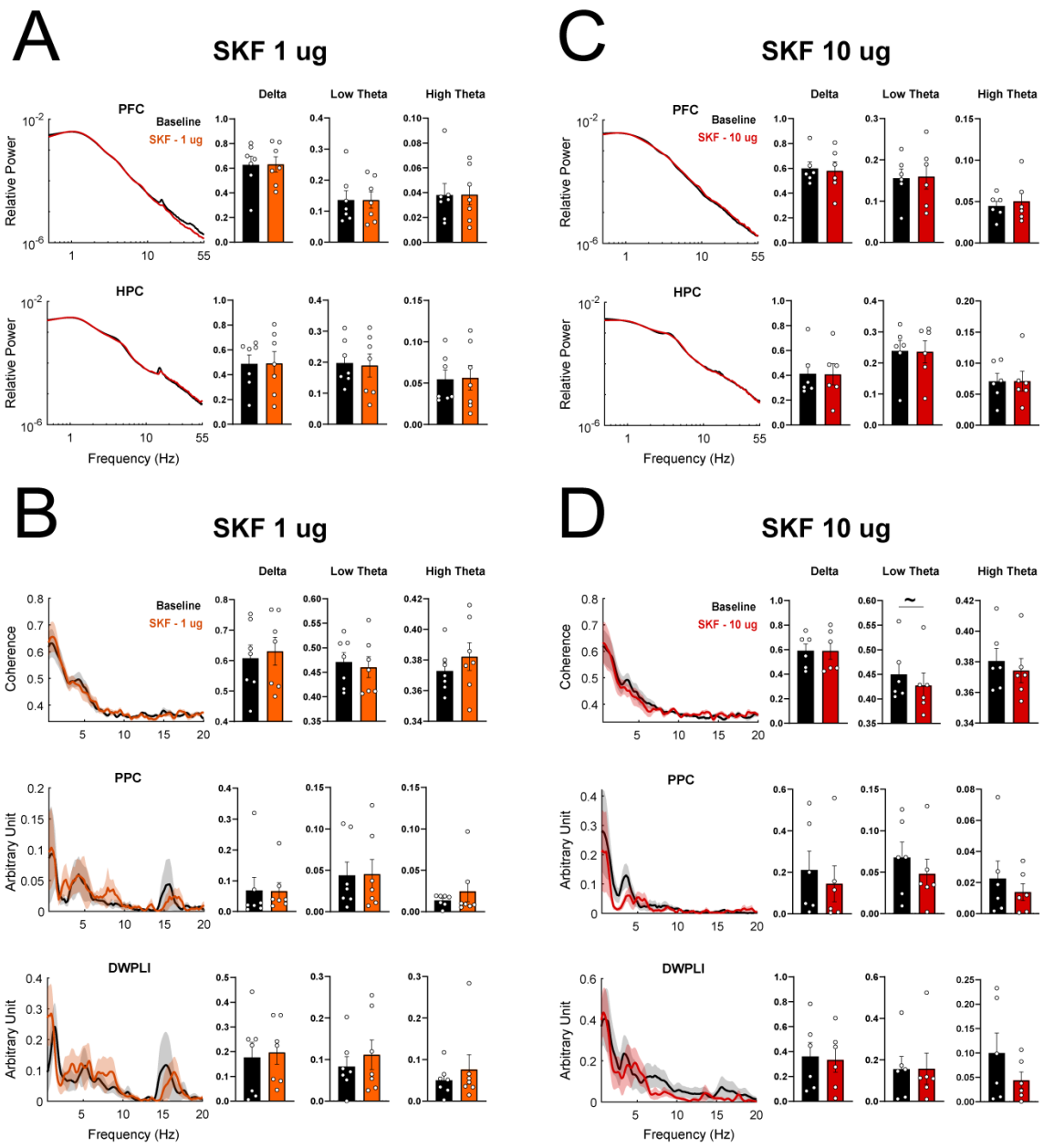

Figure S3. SKF effects on HPC-PFC connectivity. Statistical comparisons between averaged period after injection (initial period, 2-12 min) and the respective injection averaged baseline. (**A-B**) PFC and HPC averaged PSDs. (**C-D**) HPC-PFC synchronization is represented by measures of coherence (top), pairwise phase consistency (PPC, middle), and debiased weighted phase lag index (DWPLI, bottom). Data presented as mean ± SEM. ~p<0.1. The 1µg SKF dose produces no significant changes from baseline (**A, C**), while the 10µg dose only induces a decrease in coherence (HPC-PFC) in theta 3-6 Hz, with no change in the other measures (**B, D**).

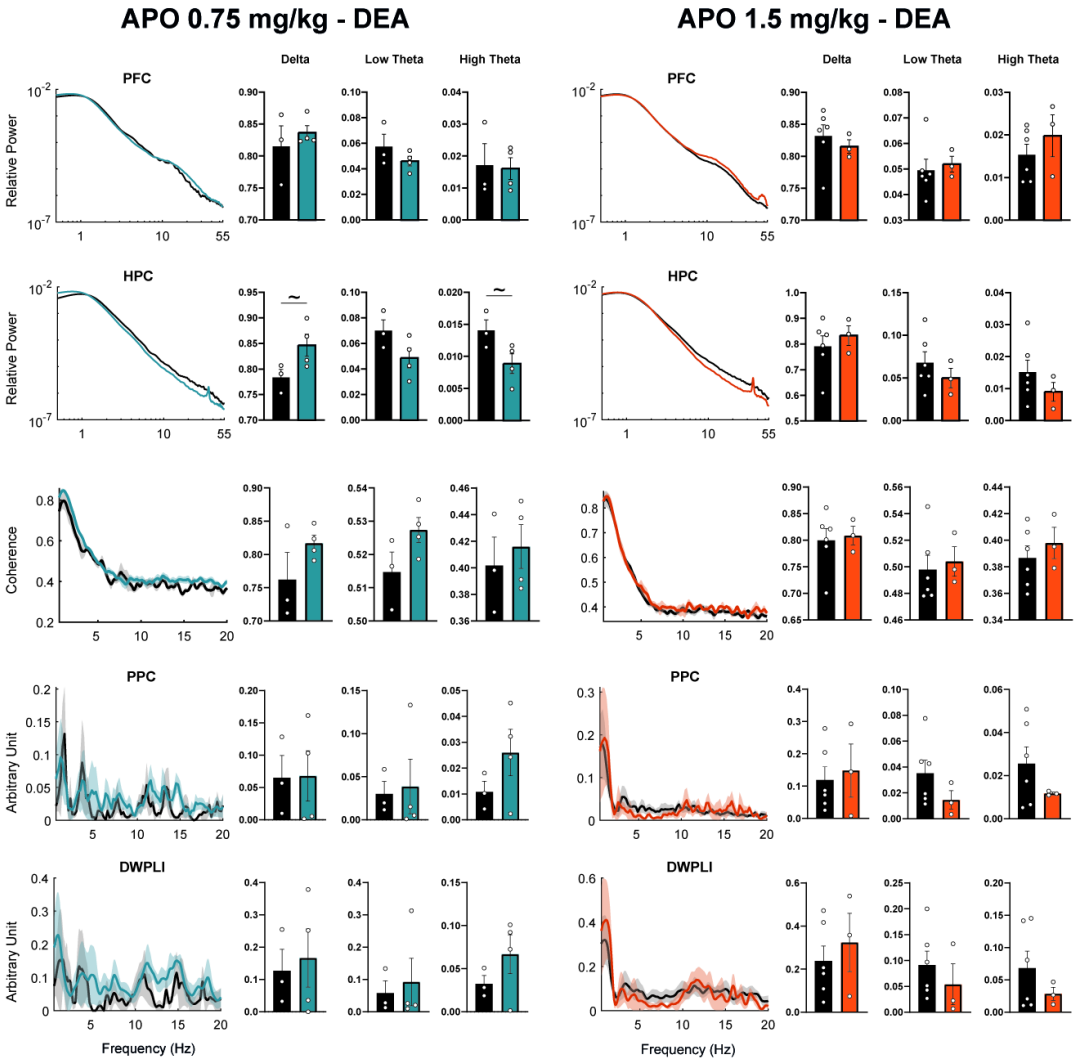

Figure S4. Effects of Apomorphine administration on HPC-PFC connectivity separated by states.

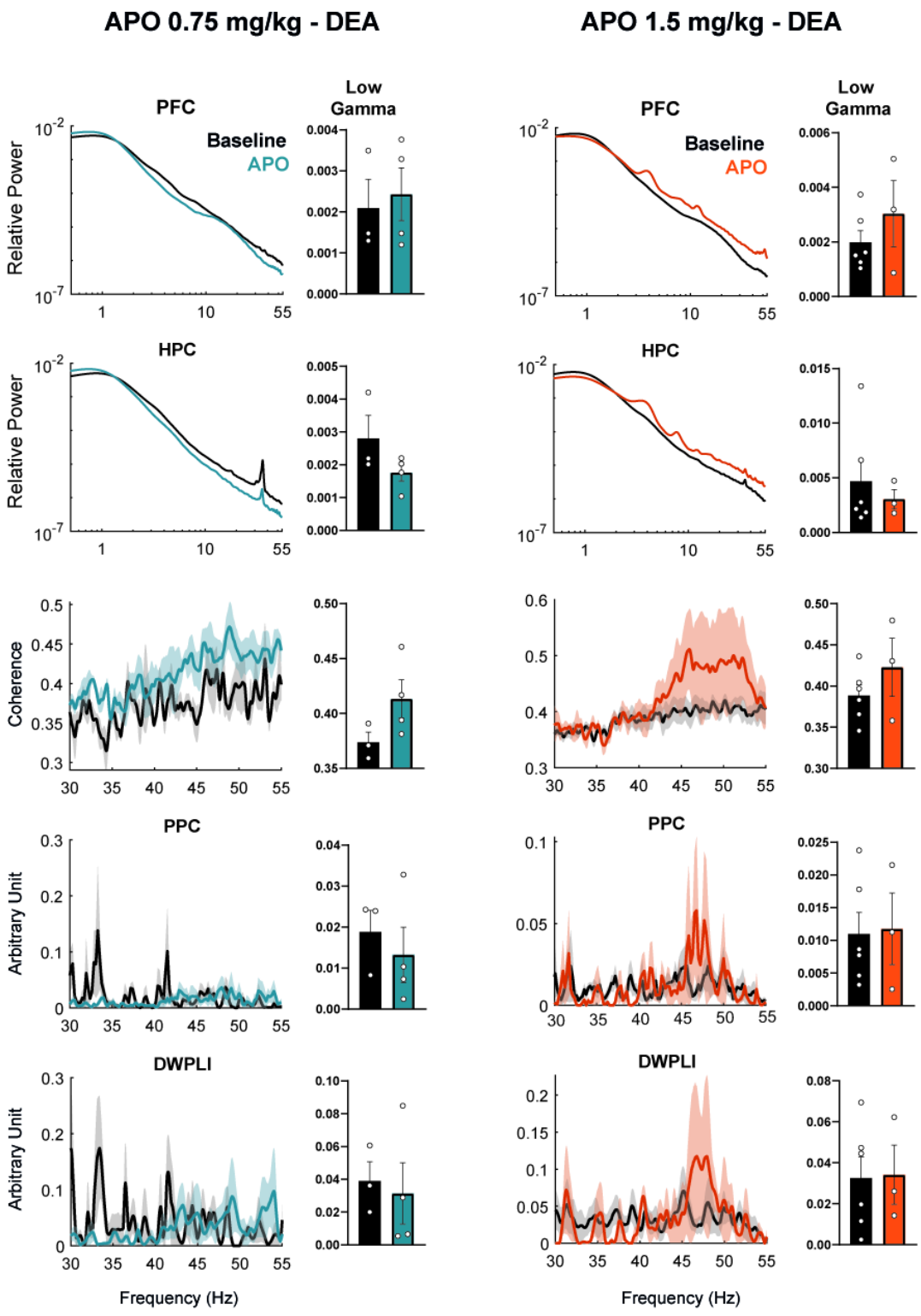

Figure S5. Effects of Apomorphine administration on HPC-PFC gamma connectivity separated by states.

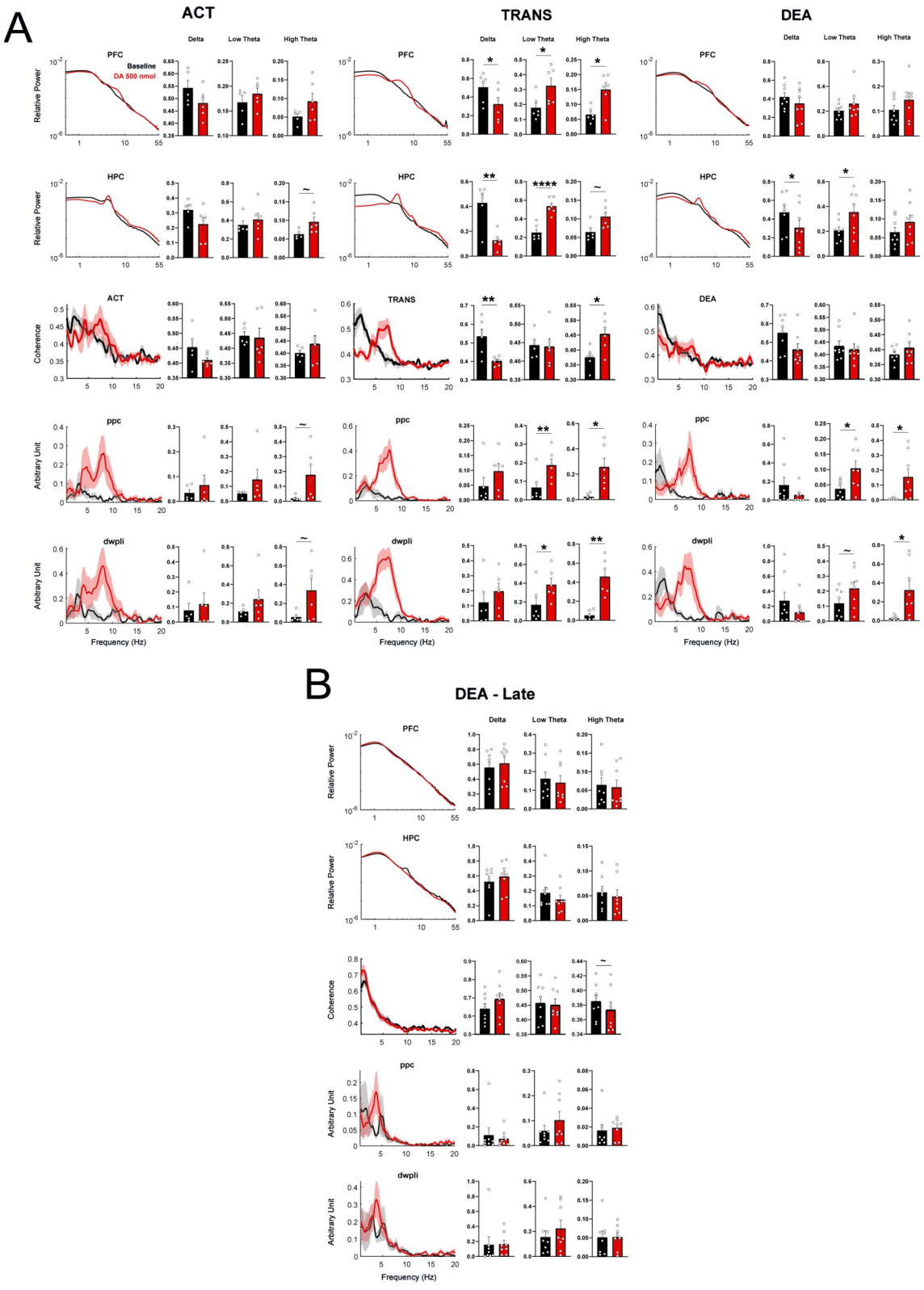

Figure S6. Effects of 500 nmol DA administration on HPC-PFC connectivity separated by states.

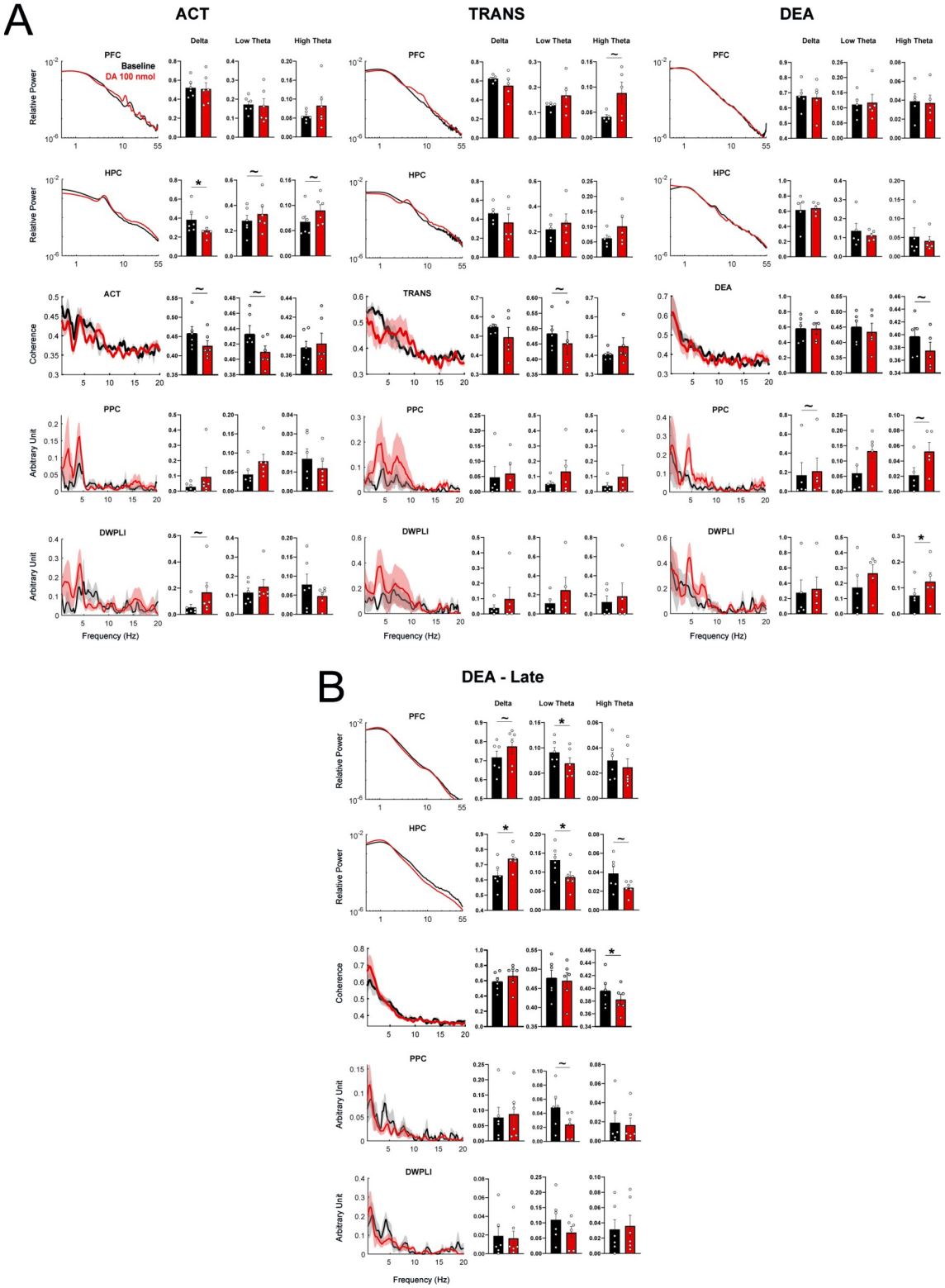

Figure S7. Effects of 100 nmol DA administration on HPC-PFC connectivity separated by states.

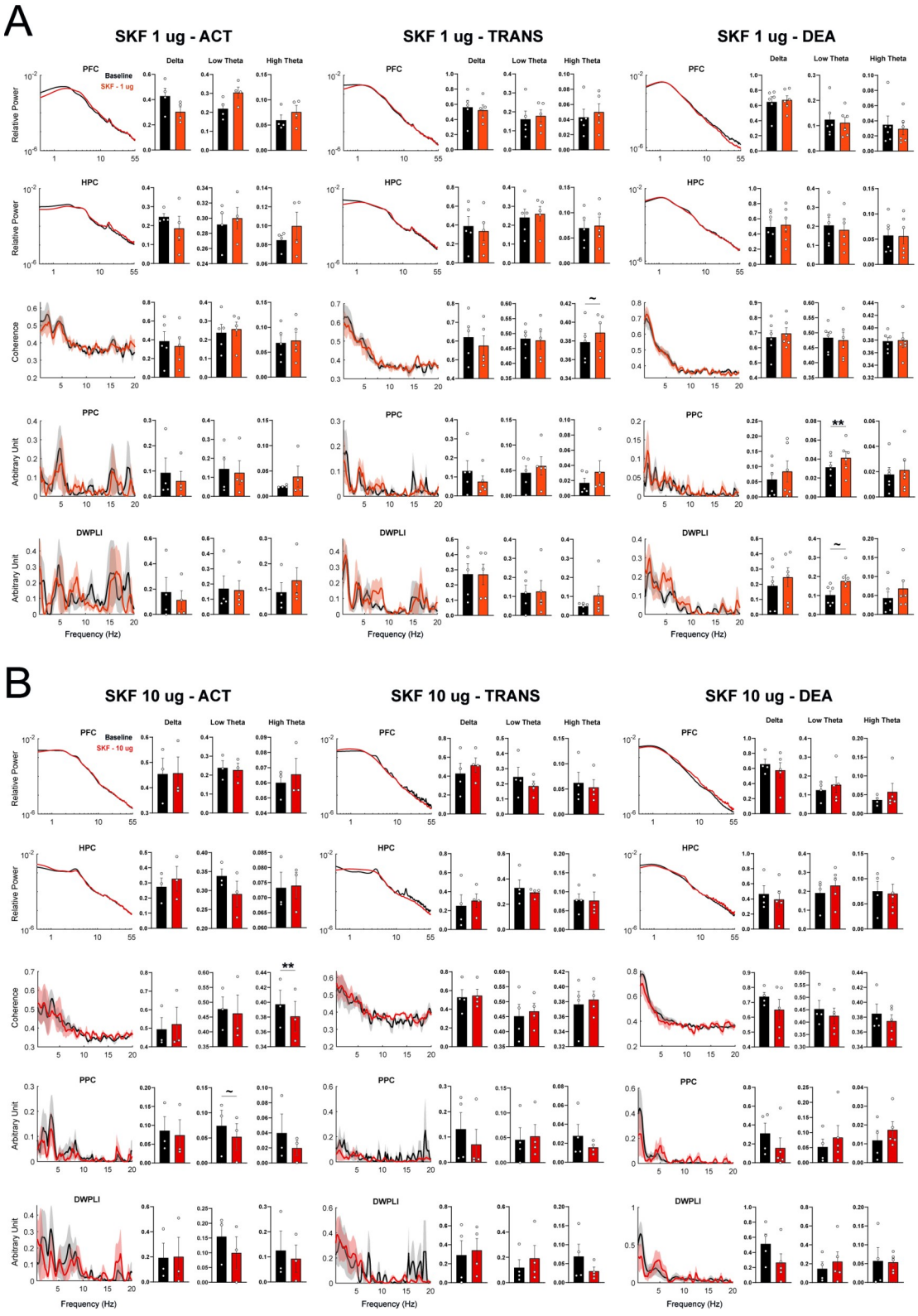

Fig S8. Effects of SKF administration on HPC-PFC connectivity separated by states.

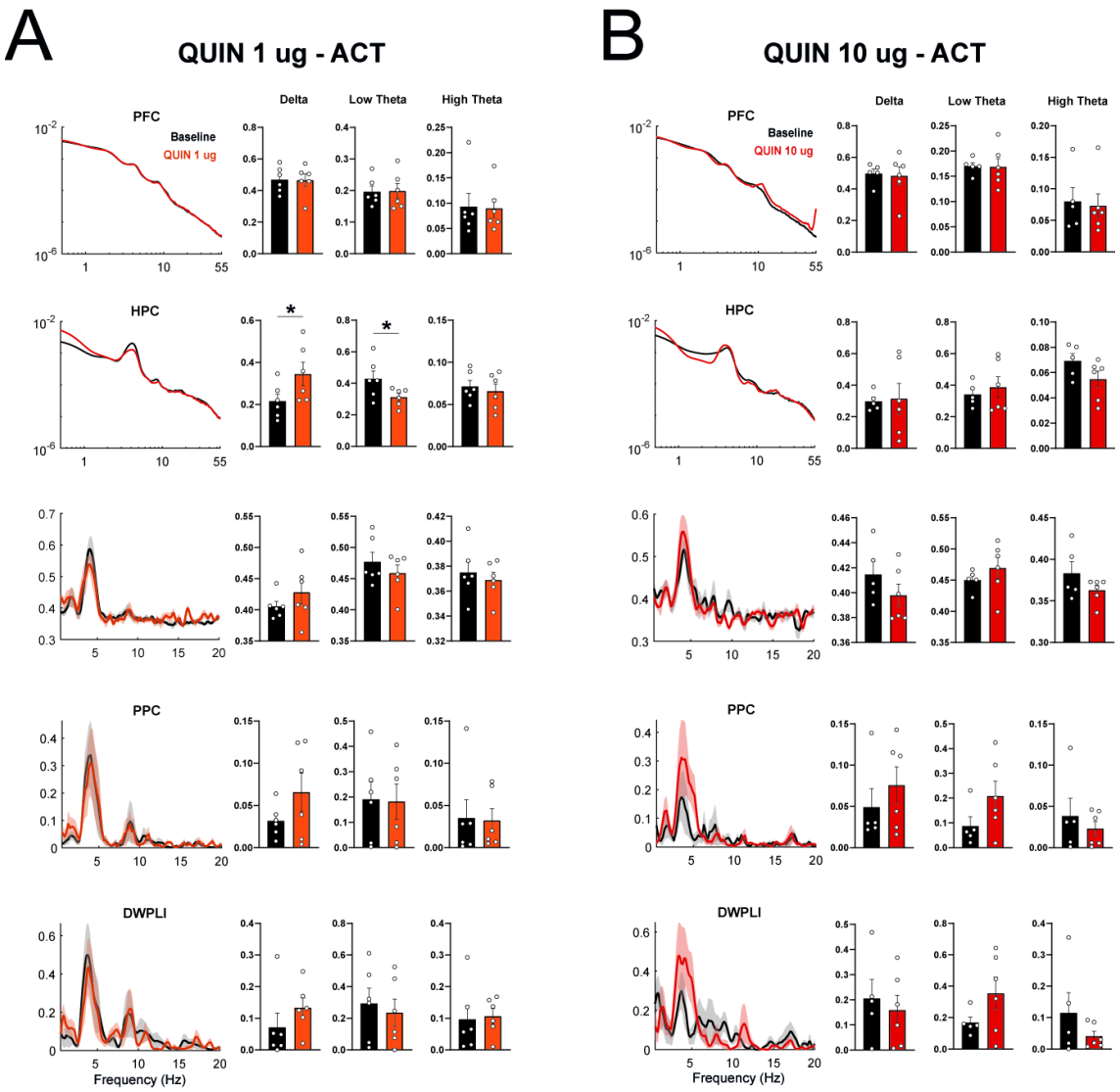

Fig S9. Effects of QUIN administration on HPC-PFC connectivity separated by states.

4. Discussão expandida

4.1. Participação dopaminérgica na regulação de teta

Em nossos resultados, observamos que a administração de DA gera oscilações teta no HPC e no PFC. Na dose mais elevada de DA, essas oscilações teta foram acompanhadas de um aumento robusto na coerência e na sincronia de fase em teta, especialmente em teta 6-10 Hz. É bem descrito na literatura que oscilações teta hipocampais existem ao menos em duas formas: uma resistente ao antagonismo muscarínico de drogas colinérgicas, como a atropina, conhecida como teta tipo 1, e outro sensível a ação dessas drogas, conhecida como teta tipo 2 (Kramis et al., 1975). Oscilações teta tipo 1 possuem frequências mais rápidas (6-10 Hz) e são características de animais em vigília, enquanto oscilações teta tipo 2 possuem frequências mais lentas (4-6 Hz) e predominam durante estados de imobilidade ou na anestesia de uretana (Sainsbury et al., 1987, Yoder & Pang, 2005). Interessantemente, nossos dados indicam que são necessárias doses elevadas de DA para a potencialização robusta de ambos os tipos de oscilações teta durante anestesia de uretana. No entanto, os mecanismos pelo qual DA influencia teta durante anestesia são ainda incertos. É bem conhecido que o principal contribuinte para a geração e manutenção do ritmo teta hipocampal é a região do septo medial (Hangya et al., 2009). Neurônios colinérgicos e GABAérgicos desta região projetam para interneurônios e células piramidais do HPC (Yoder & Pang, 2005) modulando as oscilações teta através de salvas de disparos rítmicos (Steward and Fox, 1989b, Apartis et al., 1998, Vertes & Kocsis, 1997). Estudos indicam que em geral as células colinérgicas, sensíveis a atropina, são as principais responsáveis pelo teta tipo 2, enquanto as células GABAérgicas, resistentes a atropina, regulam o teta tipo 1 (Vertes & Kocsis, 1997, Yoder & Pang, 2005). Notadamente, o septo medial recebe projeções dopaminérgicas da VTA cuja ativação promove via receptores D_1 o aumento da taxa de disparos de ambos os neurônios sensíveis ou resistentes a atropina (Fitch et al., 2006), sugerindo que neurônios colinérgicos e GABAérgicos septais são modulados por dopamina. É possível que esta seja uma via pela qual a dopamina influencia indiretamente o teta hipocampal. Esta hipótese explicaria a modulação de ambos os tipos de teta observada em nossos resultados.

Estudos computacionais e *in vitro* mostram que o teta hippocampal com pico em 8 Hz, dentro da faixa de frequência do teta tipo 1, pode ser gerado localmente por uma rede de interneurônios oriens lacunosum-moleculare (O-LM) (Rotstein et al., 2005; Gloveli et al., 2005). No entanto, essa rede depende de inputs inibitórios para que sua atividade oscilatória seja coerente (Rotstein et al., 2005) e se propague ao longo do hipocampo (Gloveli et al., 2005). É provável que o input inibitório necessário seja proveniente das projeções GABAérgicas septo-hipocampais, dado a relação destas células com a manutenção do teta tipo 1 (Yoder & Pang, 2005). Adicionalmente, é possível que através das projeções dopaminérgicas da VTA nas células GABAérgicas septo-hipocampais (Gaykema & Zaborszky, 1997), a dopamina module esse teta gerado localmente, promovendo o teta tipo 1. Esta hipótese explicaria nossos dados relativos à potencialização e ao aumento de sincronia do teta tipo 1 após injeção de dopamina.

Uma outra forma possível pela qual a dopamina poderia influenciar o teta hipocampal, e que não exclui a contribuição das vias descritas anteriormente, seria através das projeções diretas da VTA (Ghanbarian & Motamedi, 2013), do nucleus accumbens (Verney et al., 1985) ou do locus coeruleus (Kempadoo et al., 2016) no hipocampo. De fato, a dopamina pode alterar diretamente uma série de propriedades intrínsecas de neurônios hipocampais, como excitabilidade, somação temporal de potenciais pós sinápticos e transmissão sináptica de células piramidais de CA1 (para referências, veja Edelmann & Lessmann, 2018). É conhecido que receptores dopaminérgicos D_1 e D_2 são expressos por todo o hipocampo (Wei et al., 2017), inclusive no stratum lacunosum moleculare (SLM) (Goldsmith & Joyce, 1994), onde se encontram os axônios de interneurônios O-LM geradores de teta hipocampal intrínseco. Notadamente, foi mostrado in vitro que a aplicação de dopamina inibe os inputs sinápticos excitatórios da via perforante nas células do SLM, e esse efeito é parcialmente bloqueado por antagonistas D_1 ou D_2 (Otmakhova & Lisman, 1999). Em conjunto, essas evidências sugerem que a dopamina liberada diretamente no HPC pode interagir com circuitos relevantes para a geração intrínseca do teta hipocampal via receptores D_1 e D_2.

4.2. As frequências da banda teta

Um dos principais resultados observados em nosso estudo foi a promoção de oscilações no amplo espectro da banda teta por injeção de DA. Como descrito anteriormente, estudos com roedores executando tarefas cognitivas em labirintos tem revelado que frequências na faixa da banda teta (3-10 Hz) seriam responsáveis por processos cognitivos distintos. Fujisawa & Buzsáki (2011) descrevem uma frequência de teta a 4 Hz que sincroniza a atividade oscilatória HPC-PFC-VTA durante a execução de tarefa de memória de trabalho no labirinto em T. Mais recentemente, Padilla-Coreano et al. (2019) revelou que a sincronia HPC-PFC na frequência de teta a 8 Hz seria responsável por gerar e sustentar o comportamento de esquiva, e que o mesmo não foi observado em outras frequências testadas (2, 4 e 20 Hz). De fato, como apresentado e discutido por Dickson et al. (2022), a coordenação da atividade oscilatória em teta no circuito HPC-PFC é altamente dinâmica e responsiva à demanda cognitiva, de tal modo que frequências de teta se relacionam a processos específicos como manutenção de memória de trabalho e aprendizado da tarefa (4 Hz) e produção de comportamento de esquiva (8 Hz). Apesar de nosso estudo ter sido realizado em animais anestesiados, nossos dados a respeito do papel da dopamina na modulação das frequências de teta podem ser generalizados. Nesse sentido, nossos dados suportam as evidências de que a neurotransmissão dopaminérgica tem participação na coordenação dinâmica das frequências de teta e dos processos cognitivos dependentes da coordenação HPC-PFC.

5. Conclusões

Nosso estudo fornece evidências sobre o papel da dopamina e do agonismo de receptores dopaminérgicos D_1 e D_2 na regulação da dinâmica oscilatória HPC-PFC. Nossos resultados mostraram que os estados oscilatórios da anestesia de uretana são amplamente modulados pela dopamina, bem como pelo agonismo inespecífico da apomorfina e o agonismo específico de receptores D2, apresentando efeitos imediatos e tardios antagônicos entre si. Mostramos também que a dopamina induz sincronia HPC-PFC em frequências rápidas da banda teta (6-10 Hz) que não ocorrem espontaneamente nos padrões oscilatórios da anestesia de uretana. Essas evidências experimentais contribuem para uma compreensão melhor do papel dopaminérgico na coordenação das dinâmicas oscilatórias e consequente facilitação da interação HPC-PFC.

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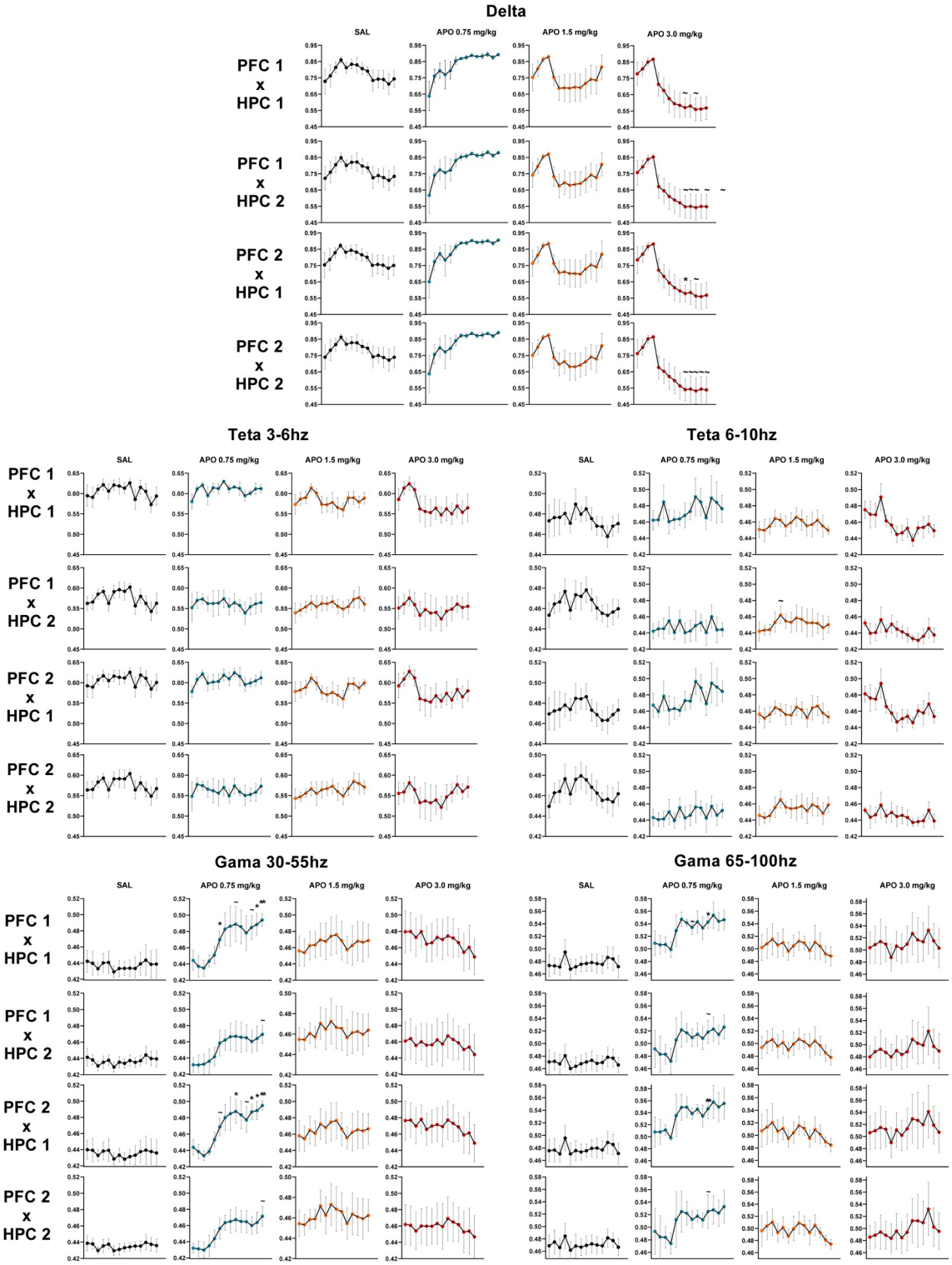
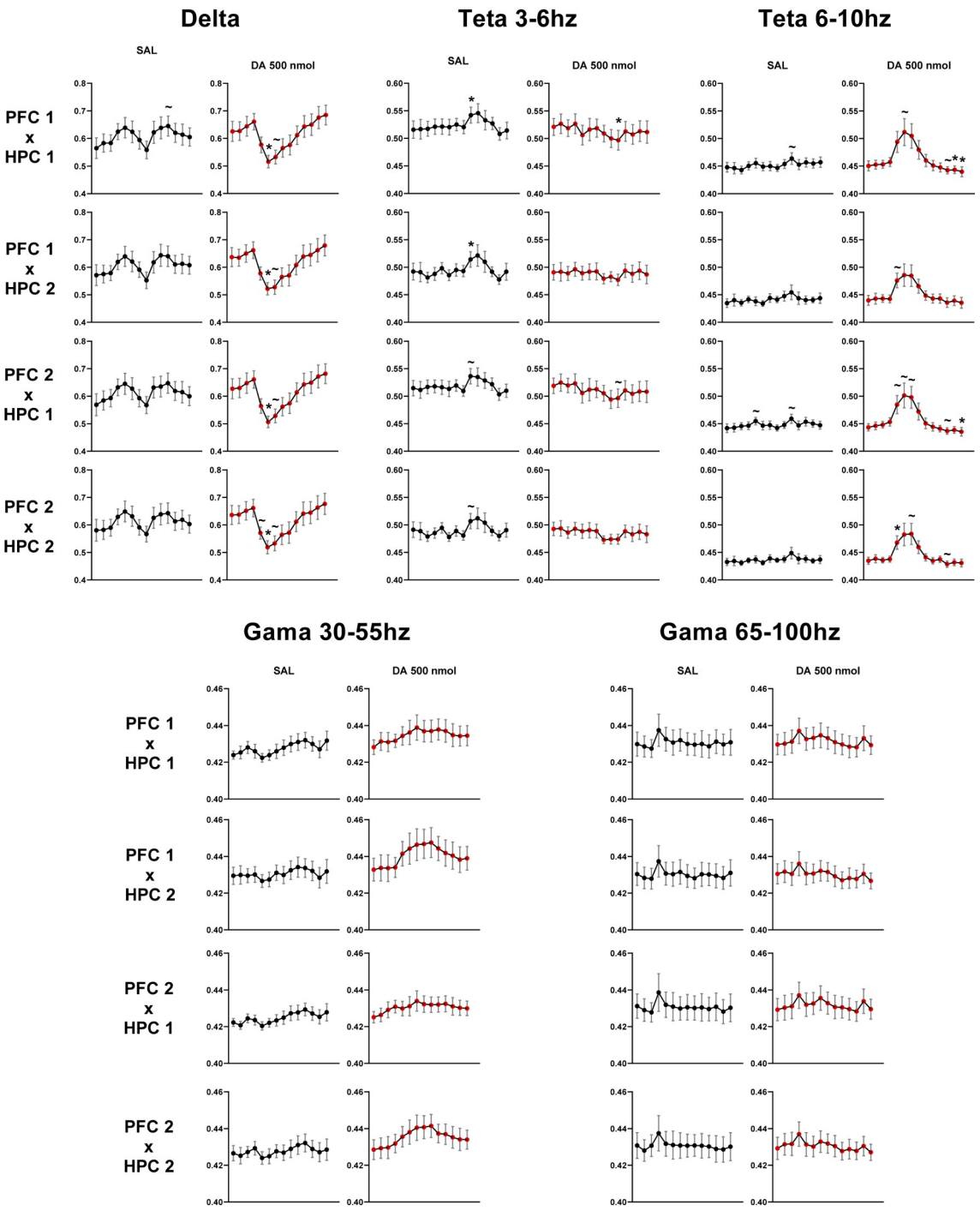
Apêndices

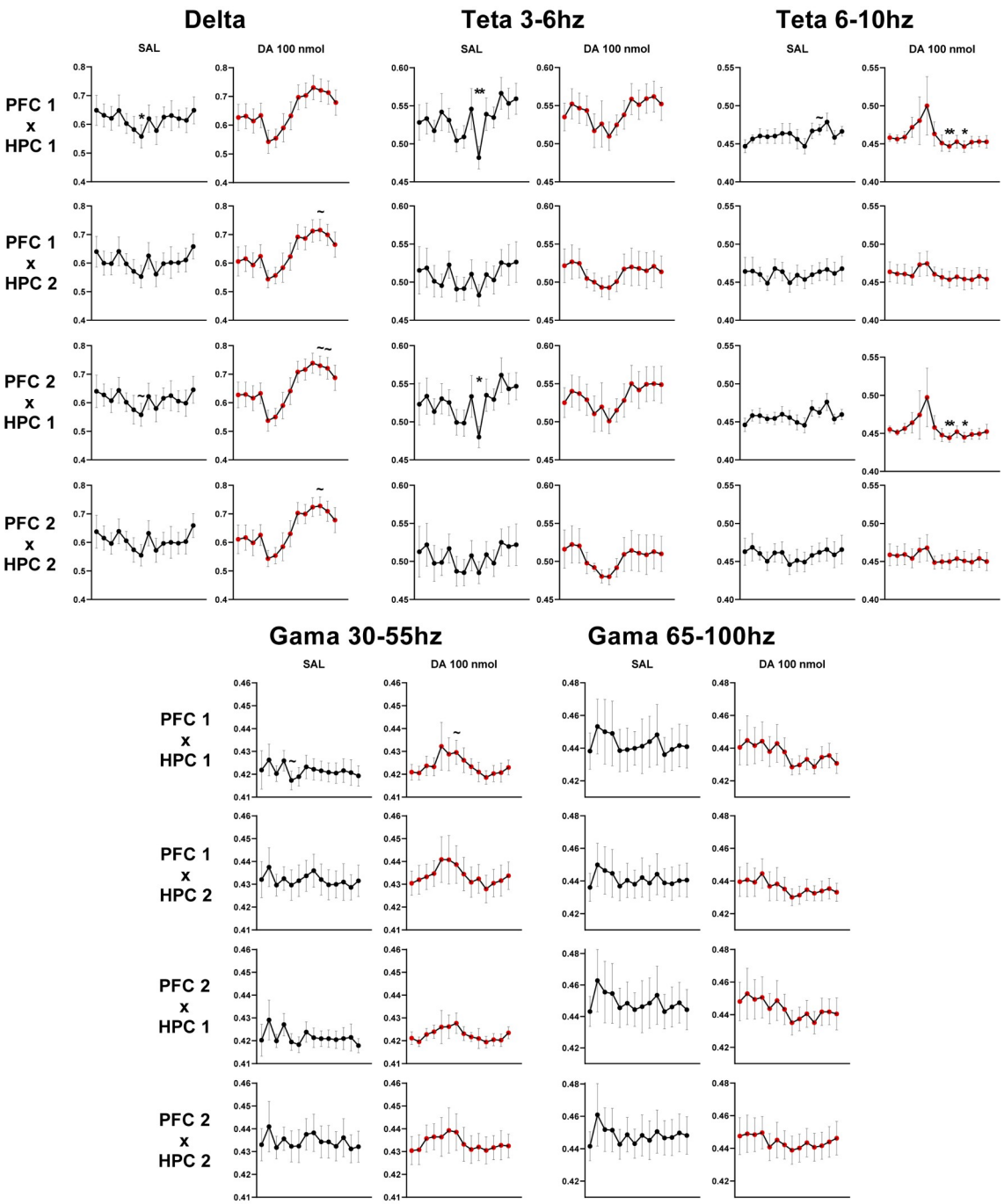
Apêndice A – Figuras extras com informações adicionais



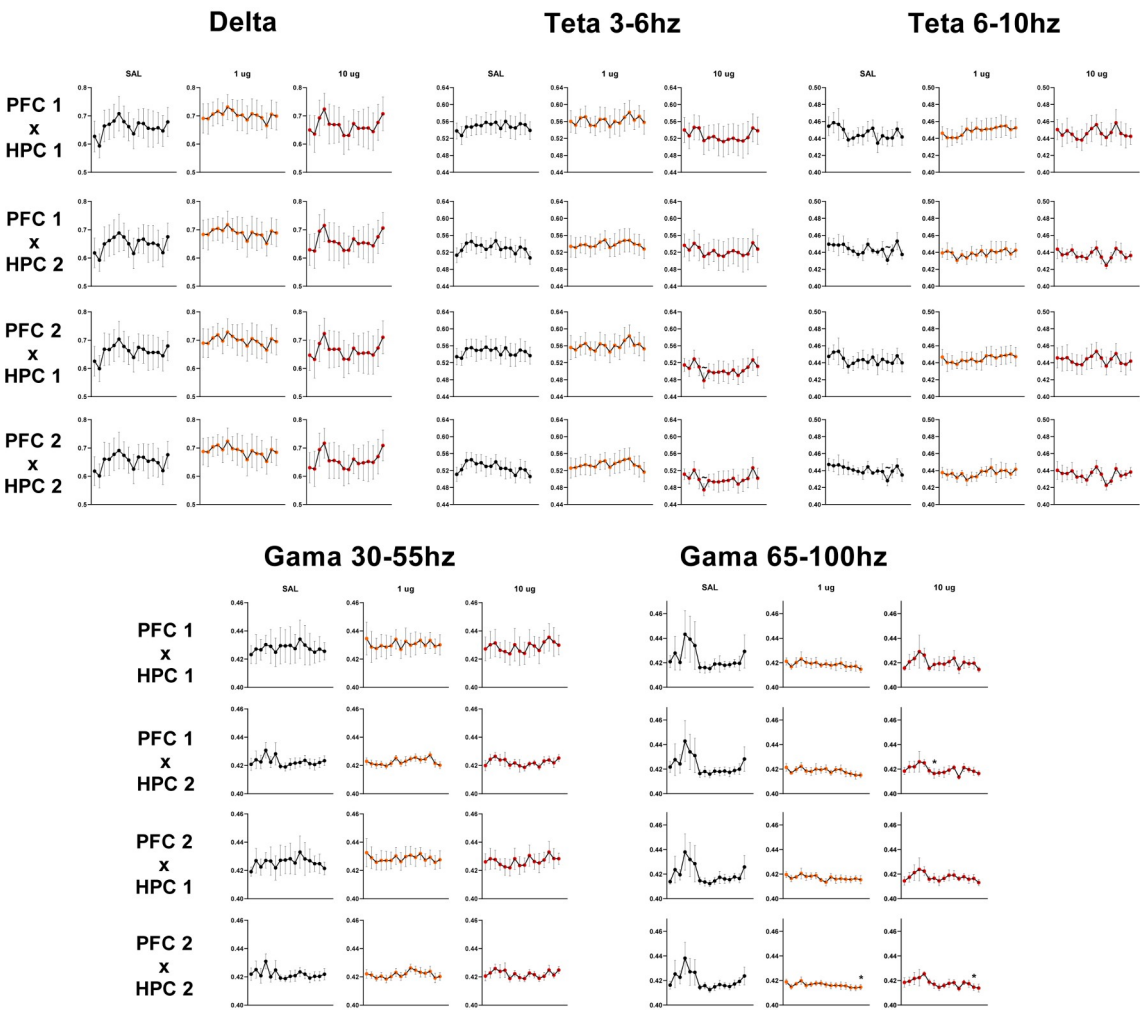
Efeitos de Apomorfina sobre a coerência espectral entre todas as coordenadas HPC-PFC registradas.



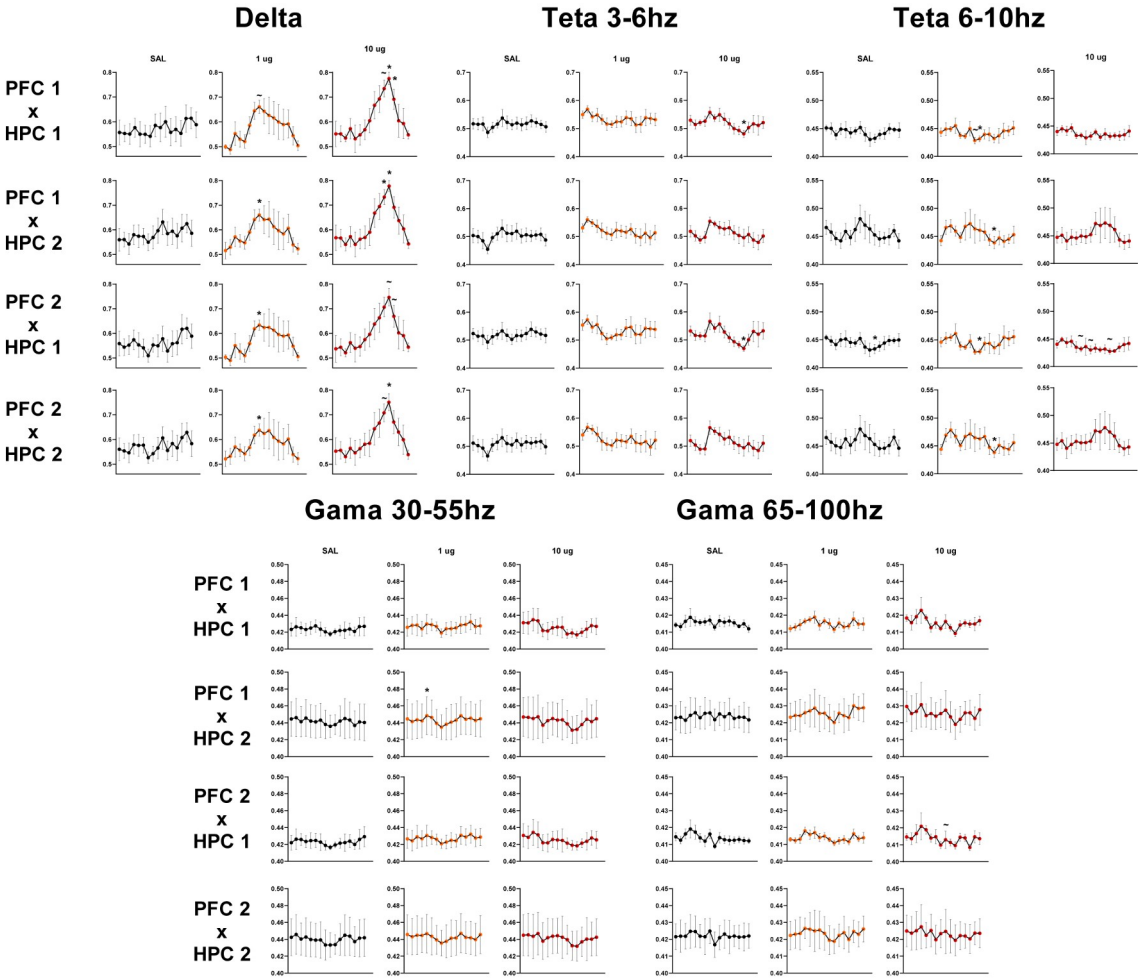
Efeitos de Dopamina 500 nmol sobre a coerência espectral entre todas as coordenadas HPC-PFC registradas.



Efeitos de Dopamina 100 nmol sobre a coerência espectral entre todas as coordenadas HPC-PFC registradas.



Efeitos de agonista dopaminérgico SKF sobre a coerência espectral entre todas as coordenadas HPC-PFC registradas.



Efeitos de agonista dopaminérgico Quinpirole sobre a coerência espectral entre todas as coordenadas HPC-PFC registradas.