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Expanding the therapeutic potential of neuro(active)steroids: a promising strategy for hyperdopaminergic behavioral phenotypes

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ABSTRACT

Imbalances in dopamine activity significantly contribute to the pathophysiology of several neuropsychiatric disorders, including addiction, ADHD, schizophrenia, impulse control disorders, and Parkinson's Disease. Neuro(active)steroids, comprising endogenous steroids that finely modulate neuronal activity, are considered crucial regulators of brain function and behavior, with implications in various physiological processes and pathological conditions. Specifically, subclasses of Neuro(active)steroids belonging to the 5α reductase pathway are prominently involved in brain disorders characterized by dopaminergic signaling imbalances. This review highlights the neuromodulatory effects of Neuro(active)steroids on the dopamine system and related aberrant behavioral phenotypes. We critically appraise the role of pregnenolone, progesterone, and allopregnanolone on dopamine signaling. Additionally, we discuss the impact of pharmacological interventions targeting 5α reductase activity in neuropsychiatric conditions characterized by excessive activation of the dopaminergic system, ranging from psychotic (endo)phenotypes and motor complications to decision-making problems and addiction.

1. Introduction

1.1. Neuro(active)steroids as neuromodulators of synaptic function

Neuro(active)steroids (NaS) constitute a broad category of endogenous steroids exerting their effects within the central nervous system (CNS), irrespective of their site of synthesis. Originating from cholesterol, these lipid mediators can be locally synthesized in various brain regions, such as the cortex, striatum, hippocampus, and hypothalamus, or can arise from peripheral sources, including adrenal glands, gonads, and placenta (Baulieu, 1998; Giatti et al., 2019; Melcangi and Panzica, 2006; Paul and Purdy, 1992; Porcu et al., 2016). Their lipophilicity enables them to readily cross the blood-brain barrier (BBB) and modulate neuronal function through interactions at multiple cellular sites. By engaging with a variety of ligand-gated ion channels, membrane and intracellular receptors, NaS act through both rapid and non-rapid signaling pathways, participating in canonical G protein-coupled receptors (GPCR) membrane signaling and/or nuclear genomic cell responses. Two of the main non-genomic targets of NaS are γ-aminobutyric acid ($GABA_A$) and N-methyl-D-aspartate (NMDA) receptors. NaS, such as allopregnanolone (AP) and allotetradeoxycorticosterone (THDOC), are potent endogenous positive allosteric modulators (PAM) of the inhibitory neurotransmitter GABA at both synaptic and extrasynaptic $GABA_A$ receptors, which binding enhances

Abbreviations: **3α-HSOR**, 3α-Hydroxysteroid Oxidoreductase; **5α-DHP**, 5α-Dihydroprogesterone; **5αr**, 5α-Reductase; **ADHD**, Attention Deficit Hyperactivity Disorder; **AP**, Allopregnanolone; **BBB**, Blood-Brain Barrier; **CNS**, Central Nervous System; **Cryo-EM**, Cryo-Electron Microscopy; **CYP450scc**, Cytochrome P450 Side-Chain Cleavage; **DAT**, Dopamine Transporter; **DHEAS**, Dehydroepiandrosterone Sulfate; DHT, Dihydrotestosterone; **GABA**, Γ-Aminobutyric Acid; **GD**, Gambling Disorder; **GPCR**, G Protein-Coupled Receptors; **IMM**, Inner Mitochondrial Membrane; **LID**, L-DOPA-Induced Dyskinesias; **NAc**, Nucleus Accumbens; **NAM**, Negative Allosteric Modulators; **NaS**, Neuroactive Steroids; **NMDA**, N-Methyl-D-Aspartate; **OMM**, Outer Mitochondrial Membrane; **ORT**, Object Recognition Test; **PAM**, Endogenous Positive Allosteric Modulators; **PCE**, Prenatal Cannabis Exposure; **PD**, Parkinson's Disease; **PFC**, Prefrontal Cortex; **PME**, Pregnenolone-Methyl-Ether; **PPD**, Postpartum Depression; PPI, Prepulse Inhibition; PREG, Pregnenolone; Pregs, Pregnenolone Sulfate; PTSD, Post-Traumatic Stress Disorder; Star, Steroidogenic Acute Regulatory Protein; THC, Δ9-Tetrahydrocannabinol; THDOC, Allotetradeoxycorticosterone; **THP**, 3α, 5α-Tetrahydroprogesterone; TM, D, Transmembrane Domain; TS, Tourette's Syndrome; VTA, Ventral Tegmental Area; σ1, Sigma-1 Receptor.

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channel activation by GABA (Akk et al., 2007; Belelli and Lambert, 2005; Bitran et al., 1991). Behavioral and electrophysiological studies demonstrate that AP and THDOC have a particular affinity for extra-synaptically located $GABA_A$ receptors incorporating the δ-subunit, which contribute to maintaining an inhibitory tonic current in response to ambient levels of GABA. Additionally, the sulfation process, catalyzed by sulfotransferase enzymes on NaS with comparable structures, confers opposing actions on $GABA_A$ and NMDA receptors via different binding sites (Bowlby, 1993; Gibbs et al., 2006; Malayev et al., 2002; Mienville and Vicini, 1989; Park-Chung et al., 1997; Spivak, 1994). For instance, a recent study combines cryo-electron microscopy (cryo-EM) assays with electrophysiology and molecular dynamics simulations to explore $GABA_A$ receptor binding sites and allosteric mechanisms for AP versus sulfated NaS. Legesse and collaborators (2023) corroborate earlier findings on the mechanism of action of PAM NaS, revealing that AP increases sensitivity to GABA and ion channel width binding at the β-α interfaces in the transmembrane domain subunit interface site on the $GABA_A$ receptor. Contrary to earlier assumptions, Negative Allosteric Modulators (NAM)-NaS, such as pregnenolone (PREG) and dehydroepiandrosterone sulfate (DHEAs), primarily target the ion channel to exert inhibitory effects on $GABA_A$ receptors. This stands in contrast to the previously proposed notion that their action occurred at sites along the receptor-lipid interface. In fact, unlike AP, which can easily diffuse through the membrane and reach its binding site in the transmembrane domain (TMD), the charged sulfate groups of these NAMs do not allow inhibition of $GABA_A$ receptors from the cytosolic side of the cell membrane, as they can only access their binding site externally. Sulfated NaS also modulate both the inhibition and excitation of NMDARs. These effects are contingent upon both the subunit composition and the structure of NaS, wherein pregnane sulfates primarily induce NMDAR inhibition, while pregnenolone sulfate (PREGs) elicits potentiation (Korinek et al., 2011; Malayev et al., 2002; Park-Chung et al., 1997, 1994). However, differently from $GABA_A$ receptors, the precise binding site of sulfated NaS on NMDA receptors remains elusive. Initially, it was assumed to be extracellular (Park-Chung et al., 1997), with the M3-M4 extracellular loop of GluN2 subunits implicated in sulfated steroid action (Horak et al., 2006). Recent studies, however, have demonstrated the involvement of both the ligand-binding and transmembrane domains of GluN subunits (Hrcka Krausova et al., 2020; Wilding et al., 2016).

Within the CNS, both neuronal and glial cells participate in NaS synthesis (Akwa et al., 1991; Robel and Baulieu, 1995). NaS operate in a

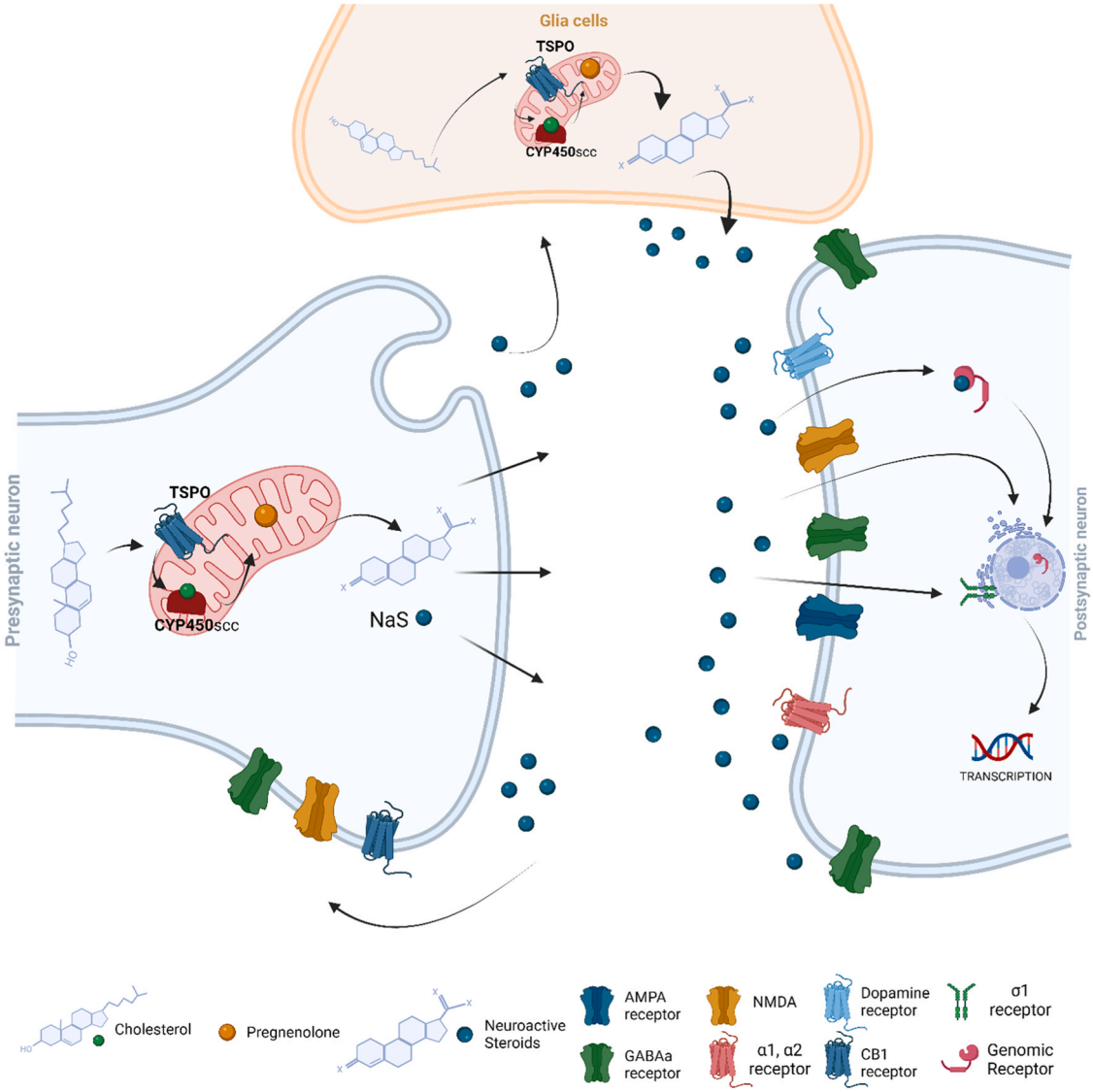

Fig. 1. Genomic and nongenomic mechanisms of neuro(active)steroids. Abbreviations: NaS, neuro(active)steroids; TSPO, Translocator protein; P450scc, cytochrome P450 side-chain cleavage (created with BioRender.com).

paracrine and/or autocrine manner to finely modulate neuronal activity. As autocrine and paracrine messengers, NaS can modulate the excitability of the same or neighboring cells through fast-acting activity, facilitating local communication between cells and synaptic components. In neurons, NaS can be synthesized by both pre- and post-synaptic terminals. Presynaptic synthesis involves their release into the synaptic cleft upon neuronal activation, where they influence synaptic transmission and neuronal excitability. Through postsynaptic release, NaS may act locally on postsynaptic receptors or diffuse back to presynaptic terminals, thereby influencing neurotransmitter release and participating in synaptic plasticity and neuronal responses to neurotransmitter signaling. Thus, NaS encompass all the core features of neuromodulators capable of modifying diverse neurotransmitter systems, including GABA (Lambert et al., 2009), glutamate (Irwin et al., 1994; Sedlácek et al., 2008), and dopamine (Dornellas et al., 2020; Motzo et al., 1996; Rougé-Pont et al., 2002), among others. NaS can both enhance and inhibit synaptic transmission mediated by these neurotransmitters, thereby adjusting the balance of excitatory and inhibitory neurotransmission in key regions involved in behavioral regulation (Fig. 1).

The ability of NaS to modulate neuronal activity of the main excitatory and inhibitory neurotransmitters makes them crucial regulators of brain function and behavior, with implications in various physiological processes and pathological conditions. For instance, their levels follow profound dynamic changes in response to acute and prolonged stress exposures; whereas acute stress increases NaS concentrations in brain and plasma, chronic stress exposures typically reduce neurosteroidogenesis (Barbaccia et al., 2001; Biggio et al., 2014; Pisu et al., 2022; Serra et al., 2000). Additionally, NaS fluctuate throughout all the reproductive phases, including pregnancy, puberty and the ovarian cycle, contributing to emotional regulation and behavioral changes observed during these critical biological processes (Concas et al., 1998; Fadalti et al., 1999; Kimball et al., 2020; Luisi et al., 2000; Mellon and Vaudry, 2001; Pisu et al., 2022; Stomati et al., 1998; Wang et al., 1996).

Dysregulations of neurosteroidogenic pathways have been documented across a spectrum of neurological and psychiatric disorders, spanning from Parkinson's and Alzheimer's disease to depression, anxiety disorders, and schizophrenia (Bourque et al., 2024; Crowley and Girdler, 2014; di Michele et al., 2013; Dubrovsky, 2005; Eser et al., 2008; Heydari and Le Mellédo, 2002; Luchetti et al., 2023, 2011; Luscher et al., 2011; MacKenzie et al., 2007; Marx et al., 2006; Weill-Engerer et al., 2002). Noteworthy, compelling preclinical and clinical evidence suggests that specific subclasses of NaS, i.e. those belonging to the 5α reductase pathway, are prominently involved in brain disorders characterized by dopaminergic signaling imbalances (Table 1). Dopamine plays a pivotal role in fundamental neurobehavioral functions such as cognition, motivation, and motor control. Alterations of dopamine neurotransmission contribute to numerous neuropsychiatric disorders including addiction, attention deficit hyperactivity disorder (ADHD), schizophrenia, impulse control disorders, and Parkinson's disease (PD) (Cardinal et al., 2001; Castellanos and Tannock, 2002; Howes et al., 2017; Klein et al., 2019; Peters et al., 2020; Viggiano et al., 2002; Wang et al., 2017). Pathological imbalances in NaS synthesis and metabolism have been consistently observed in the abovementioned conditions. Although the precise mechanisms driving these changes remain elusive, the available evidence suggests that brain NaS dysregulation may be either the result of compensatory protective mechanisms, direct causal or contributing factor exacerbating pre-existing pathophysiological processes. Therefore, gaining insight into how NaS participate in the etiopathogenesis of dopamine-relevant brain disorders may potentially unveil novel therapeutic interventions based on neurosteroidogenic pathways. In this context, the specific classes of NaS associated with the 5α reductase (5αR) pathways (as detailed in the next paragraphs) have been shown to exert beneficial effects on aberrant behavioral phenotypes driven by hyperdopaminergic states. Preclinical studies suggest that NaS rescue properties appear to be mediated at different levels of dopamine neurotransmission, and engage multiple dopaminergic receptors and the regulation of pre- and post-synaptic events.

To the best of our knowledge, this review represents the first comprehensive examination of NaS neuromodulatory effects on dysfunctional dopamine system and related aberrant behavioral phenotypes, with a particular emphasis on the subclass synthesized via the 5α reductase pathway. Recent preclinical and clinical investigations suggest that these 5αR-related NaS exhibit notable efficacy in ameliorating behavioral outcomes associated with hyperactivation of the mesostriatal dopamine system. In this review, we delve into how their modulatory actions on dopamine signaling may offer advantages over conventional pharmacotherapies, which primarily act through dopamine receptor blockade, and often lead to pronounced side effects and patients' nonadherence. We also discuss the potential therapeutic implications and limitations of NaS-based therapies targeting dopamine-related neuropsychiatric disorders. Lastly, we emphasize how understanding the precise neurobiological mechanisms underlying NaS-mediated modulation of dopamine signaling and associated behaviors is crucial for realizing clinical applications for these specific subclasses of NaS.

1.2. *From cholesterol to allopregnanolone: the 5α reductase pathways*

The first step of steroidogenesis is the transfer of cholesterol from the outer (OMM) to the inner mitochondrial membrane (IMM), (Papadopoulos and Miller, 2012). Cholesterol, sourced from endogenous synthesis or from lipoprotein breakdown, serves the rate-limiting step in synthesizing all the class of steroids. Its transport across mitochondrial membranes is mediated by the cooperation of two crucial importer proteins, namely steroidogenic acute regulatory (StAR) protein and translocator protein (18 kDa, TSPO). While the mechanism involved in this process has not been fully elucidated yet, StAR appears to initiate cholesterol transfer into mitochondria (Stocco, 2000). It is located in the cytoplasm and acts as a shuttle protein binding to cholesterol molecules, and facilitating their movement from the OMM to the IMM. To efficiently anchor cholesterol to the OMM and to promote its translocation towards the IMM, StAR necessitates to interact with TSPO, a high-affinity cholesterol-binding protein located on the OMM. The role of TSPO is to facilitate the movement of cholesterol across the OMM, serving as a binding site for StAR and assisting the initial steps of cholesterol transfer into mitochondria (Miller and Bose, 2011).

Within the mitochondria, cholesterol undergoes a series of enzymatic conversions catalyzed by cytochrome P450 side-chain cleavage (CYP11A1, CYP450scc), leading to the formation of PREG, the precursor for the synthesis of all NaS. PREG is then converted to progesterone within the cytosol by 3β-hydroxysteroid dehydrogenase enzyme. Subsequently, progesterone undergoes enzymatic modifications by 5α reductase (5αR), whose reaction is the rate-limiting step in the synthesis of 3α, 5α steroid derivatives (Bortolato et al., 2013). Among the five 5αR isoenzymes, only the first two, namely 5αR1 and 5αR2, play major roles in neurosteroidogenesis. While the expression of both isoenzymes is widely distributed across most key regions of the adult rat brain (Castelli et al., 2013; Torres and Ortega, 2003), they differ in expression patterns and cellular localization. In rodents, the 5αR1 is present in the majority of forebrain regions, and is localized in neurons oligodendrocytes, microglia, type 1 astrocytes, and Schwann cells (Celotti et al., 1992; Normington and Russell, 1992). The type 2 isoform is widely expressed throughout the brain, spanning from the forebrain to the brainstem and cerebellum of the adult rat, and is localized in neurons, but not in glial cells (Castelli et al., 2013). Although with different affinity, 5αR1 and 5αR2 convert progesterone into the 5α-dihydro-derivatives, 5α-dihydroprogesterone (5α-DHP). The product of this 5αR reaction serves as a substrate for 3α-hydroxysteroid oxidoreductase (3α-HSOR), enzymes that transform 5α-DHP to 3α, 5α-tetrahydroprogesterone (THP; also known as allopregnanolone, AP) (Fig. 2). Thus, AP acts as the final product of the 5α, 3α metabolic pathway, originating from PREG and

Table 1
Clinical and preclinical evidence reporting beneficial effects of 5αR-related neuro(active)steroids on hyperdopaminergic-associated brain disorders/(endo)phenotypes.

Brain disorders	NaS-based drug	Patients	Treatment	Results	Adverse Events	References
Bipolar Disorders	Pregnenolone	Men and Women	50 mg/day or 100 mg/day for 8 weeks	Significant beneficial effects on depression and mania but not on cognition in unipolar and bipolar depressed patients with a history of substance abuse	Well-tolerated with minimal adverse events	(Osuji et al., 2010)
	Pregnenolone	Women	100 mg/day, titrated to 300 mg/day at week 2, and 500 mg/day at week 4	Depression remission rates significantly higher after pregnenolone treatment (61 % vs 37 %)	Well-tolerated with minimal adverse events	(Brown et al., 2014)
Cocaine use disorder	Pregnenolone	Men and Women	300 mg/day or 500 mg/day	Reduction of cocaine craving and anxiety	Not mentioned	(Milivojevic et al., 2022)
	Progesterone	Men and Women	400 mg/day		Reduction of negative emotion in women, but not men, following exposure to stress	
					Well-tolerated, with mild levels of transient side effects	(Fox et al., 2013)
Gambling disorder	Finasteride	Men	5 mg/day for 2 weeks	Reduction in interest in gambling corroborated by Y-BOCS score	Well tolerated	(Bortolato et al., 2012)
Major Depressive disorder	Dutasteride	Men	0.5 mg/day for 1–49 months	Increase in depressive symptoms at all intervals excluded >48 months	No mentioned	(Garcia-Argibay et al., 2022)
	Finasteride	Men	1 mg/day for 1–49 months	Increase in depressive symptoms at all time intervals investigated	No mentioned	
Zuranolone		Men and Women	30 mg/day for 14 days or 20 mg /day after adverse effects or reported sedation	Significant improvement in depressive symptoms	No serious adverse events	(Gunduz-Bruce et al., 2019)
		Men and Women	30 mg/day for 2 weeks	Significant improvement in depressive symptoms	No serious adverse events	(Suthoff et al., 2022)
			30 mg/day for 2 weeks	Significant improvement in depressive symptoms	No serious adverse events	(Arnaud et al., 2021)
Parkinson disease	Zuranolone	Men and Women	20 mg (I/II days), 30 mg (III day) for 1 week	Improvement of tremor and motor symptoms	Well-tolerated	(Bullock et al., 2021)
Post-Partum Depression	Brexanolone (Zulresso)	Women	I.V. infusion (60 h)	Improvement in depressive symptoms at the end of the first infusion	Sleepiness, dry mouth, loss of consciousness and flushing	Approved on March 19, 2019 (Epperson et al., 2023; S. Kanes et al., 2017; S. J. Kanes et al., 2017, 2017)
	Zuranolone (Zurzuvae)	Women	50 mg/day for 14 days	Improvement in the core symptoms of depression	Drowsiness, dizziness, diarrhea, fatigue, nasopharyngitis, and urinary tract infection	Approved on August 04, 2023 (Deligiannidis et al., 2023)
Schizophrenia	Pregnenolone	Men and Women	100 mg/day for 2 weeks, 300/day for 2 weeks, 500 mg/day for 4 weeks	Significant reduction in negative symptoms	Well-tolerated with minimal adverse events	(Marx et al., 2009)
		Men and Women	100 mg/day for 2 weeks, 300/day for 2 weeks, 500 mg/day for 4 weeks	Improvements in functional capacity but not in cognitive symptoms	Well-tolerated	(Marx et al., 2014)
		Men and Women	50 mg/day for 8 weeks	Reduction of PANSS negative scale and SANS domain scores	Well-tolerated without clinically significant changes	(Kreinin et al., 2017; Ritsner et al., 2014)
	Finasteride	Men	5 mg/day for 24 days	Improvement in psychotic symptoms, general and negative symptoms.	No significant side effects	(Koethe et al., 2008)
Tourette Syndrome	Finasteride	Men	5 mg/day for 28 weeks	Reduction in Y-GTSS and Y-BOCS score	Well-tolerated	(Bortolato et al., 2007)
		Men	5 mg/day for 18 weeks	Reduction in global severity, total, motor, and phonic tics. Significant reduction in Y-BOCS total and compulsion in patients with obsessive–compulsive comorbid symptoms	Two patients complained of a reduction in libido and occasional difficulty in achieving erection.No neuropsychiatric, metabolic, or endocrine side effects	(Muroni et al., 2011)
Animal models	NaS-based drug			Treatment	Results	References
Cannabis use disorder	Pregnenolone			2–6 mg/kg S.C.	Rescue of THC-induced food-intake and memory impairments in Wistar rats and C57BL/6 N mice.	Vallée et al., (2014))

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Table 1 (*continued*)

Brain disorders	NaS-based drug	Patients	Treatment	Results	Adverse Events	References
				6 mg/kg, S.C.	Rescue of psychotic-like effects and related endophenotypes in mice	(Busquets-Garcia et al., 2017)
				6 mg/kg S.C.	Rescue of synaptic defects and dopaminergic activity and behavior in PCE offspring	(Frau et al., 2019)
Cocaine use disorders	Progesterone			2 /kg mg0.5 mg/kg S.C. for 3 days	Reduction of cocaine-primed reinstatement in female, but not male rats	(Anker et al., 2009)
	Allopregnanolone			15 or 30 mg/kg S.C. for 3 days	Reduction of cocaine-primed reinstatement in female, but not in male rats	(Anker et al., 2009)
Depression	Allopregnanolone			5 μg/rat I.C.V. 0.5 or 0.05 μg/side	Reduction of immobility in Forced Swim Test	(Almeida et al., 2018)
				2 μg/0.3 μl	Increase in latency to first immobility and reduction in total immobility time in the forced swim test	(Rodrìguez-Landa et al., 2007)
	Progesterone			0.001, 0.01 and 0.1 M	Reduction of both time of immobility and number of immobility periods	(Estrada-Camarena et al., 2002)
Gambling disorder	Finasteride			25–50 mg/kg I.P.	countered the elevation in probability-discounting in reserpine-pramipexole model of pathological gambling	(Floris et al., 2022)
Opioid use disorder	Ganaxolone			10 mg/Kg S.C.	Reduction of contextual fear on SI mice	(Pinna and Rasmusson, 2014)
	Finasteride			5 nM in zebrafish, 50 mg/kg, IP in rats	Reduction in opioid intake in zebrafish and rat self-administration paradigms	(Bosse et al., 2021)
Parkinson disease	Pregnenolone			6, 18, 36 mg/kg, S.C. or 3 weeks	Pregnenolone counteracts LIDs development in 6-OHDA-lesioned rats without affecting the therapeutic efficacy of L-DOPA	(Corsi et al., 2023)
	Allopregnanolone			10 mg/kg S.C., once a week for 2 weeks	Normalization of the MPTP lesion-induced effects on motor performance, number of TH-expressing neurons in the SN, expression of TH protein, and levels of NE in the SN and midbrain.	(Adeosun et al., 2012)
				5,20 mg/kg S.C. for 2 months	AP enhances learning and memory in 6-OHDA model of Parkinson's disease in rats.	(Nezhadi et al., 2016)
	Finasteride			30 or 60 mg/kg, IP	Finasteride significantly reduces development and expression of dyskinesia induced by l-DOPA in 6-OHDA-lesioned rats without impacting the therapeutic effects of L-DOPA	(Frau et al., 2017)
	Dutasteride			15 or 30 mg/kg, IP	Dutasteride counteract dyskinesia without impacting the therapeutic effects of L-DOPA	(Fanni et al. 2019)
Schizophrenia	Pregnenolone			60 mg/kg for 2 weeks	Reduction of positive schizophrenia-like phenotypes and cognitive deficits in DAT-KO mice	(Wong et al., 2012)
	Pregnenolone sulfate			20 mg/kg or 40 mg/kg or 80 mg/kg S.C. for 10 days	Suppression of hyperlocomotion and behavioral stereotypes, and rescue of PPI deficits in DAT-KO mice. Long-term administration of 40 mg kg−1 PREGs alleviated the cognitive deficits of DAT-KO mice in the novel object recognition and social transmission of food preference paradigms	(Wong et al., 2015)
	Progesterone			10 mg/kg, S.C.	Progesterone dampens the hyperactivity, anxiety-like behaviors and PPI deficits in DAT-KO mice.	(Frye and Sora, 2010)

(*continued on next page*)

Table 1 (*continued*)

Brain disorders	NaS-based drug	Patients	Treatment	Results	Adverse Events	References
Tourette syndrome	Allopregnanolone			5–15 mg/kg, I.P.	Exacerbation of TS-like manifestations in D1CT−7, but not wild-type littermates; these effects are countered by haloperidol	(Mosher et al., 2017)
	Finasteride			25–50 mg/kg, I.P.	Reduction of TS-like manifestations in D1CT−7	(Mosher et al., 2017)
	Isoallopregnanolone			5–10 mg/kg, S.C.	Reduction of tic-like behaviours induced by stress in D1CT−7 mice, akin to haloperidol and finasteride; IsoAP rescues the enhancement of tic-like behaviours induced by AP	(Cadeddu et al., 2020)
Sensory gating disorders	Abiraterone			10,25,50 mg/kg, I.P. 1 μg/μl I.C.V.	Normalization of the PPI deficits induced by the DA receptor agonist apomorphine	(Frau et al., 2014)
	Finasteride			10 μg/1 μl I.C.V., 0.5 μg/0.5 μl/side (multiple brain regions)	Prevention of the apomorphine-mediated PPI deficits by finasteride I.C.V and accumbens (shell and core) infusions; finasteride prevents PPI deficits produced by amphetamine and apomorphine in gonadectomized rats	(Devoto et al., 2012)
				25–50 mg/kg, I.P.	Finasteride rescues PPI deficits induced by the full D(1)-like receptor agonist SKF−82958 but not apomorphine in C57BL/6 mice	(Frau et al., 2013)

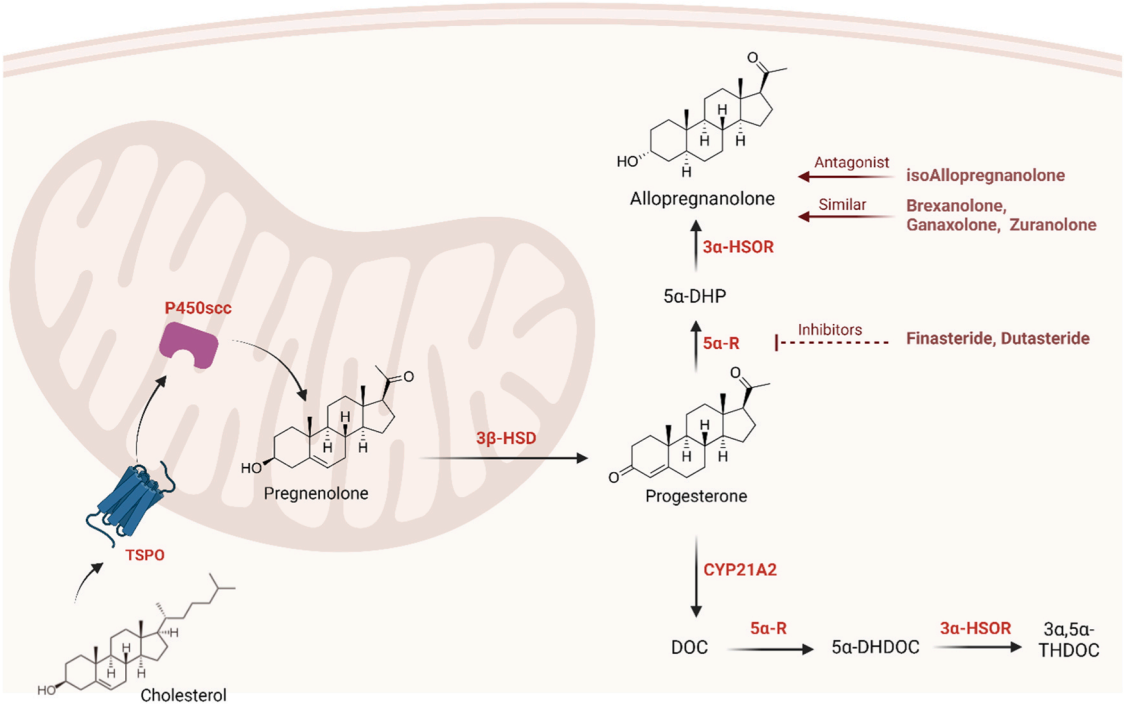

Fig. 2. Biosynthesis of neuro(active)steroids mediated by 5α reductase pathway, from pregnenolone to allopregnanolone. Abbreviations: TSPO, Translocator protein; P450scc, cytochrome P450 side-chain cleavage; 3β-HSD, 3β-hydroxysteroid dehydrogenase; 5αR, 5α reductase; 3α-HSOR, 3α-hydroxysteroid oxidoreductase; CYP21A2, steroid 21-hydroxylase; DOC, deoxycorticosterone; 5α-DHDOC, 5α-dihydro deoxycorticosterone; 3α,5α-THDOC, 3α,5α-tetrahydrodeoxycorticosterone; 5α-DHP, 5α-dihydroprogesterone; Allopregnanolone, 3α,5α-tetrahydroprogesterone (created with BioRender.com).

progressing through progesterone.

AP is mainly synthesized in the brain, although other tissues, including the ovaries (Cáceres et al., 2024), the placenta (Vacher et al., 2021) and adrenal glands (Almeida et al., 2018) have been demonstrated to have steroidogenic capacity. AP is synthesized in the corpus luteum throughout the menstrual cycle, reaching its peak levels during the luteal phase under the influence of the luteinizing hormone (LH). During the second half of gestation, the placenta produces

significant amounts of AP to support neurodevelopmental processes in the fetus, to stabilize maternal mood, and to regulate maternal stress response. After birth, maternal AP levels can drop abruptly, thereby leading to a postpartum depression (PPD) in susceptible mothers, as well as long-term adverse neurobehavioral outcomes in offspring (Pinna et al., 2022). Similarly, in individuals with low resilience, persistent stress exposures may disrupt the responsiveness of the hypothalamic-pituitary-adrenal (HPA) axis, resulting in blunted synthesis of AP from the adrenal glands and onset of psychiatric conditions, such as major depressive disorder (MDD) and post-traumatic stress disorder (PTSD) (Almeida et al., 2021).

In addition to the conversion of progesterone into DHP, it is important to underline that 5αR isoenzymes also catalyzes other important processes, including the conversion of testosterone into the potent androgen dihydrotestosterone (DHT) and the degradation of cortisol and corticosterone into their 5α-reduced metabolites, which are less potent glucocorticoid receptor agonists (McInnes et al., 2004). For these properties in reducing DHT, the 5αR inhibitors finasteride and dutasteride are currently prescribed for the treatment of benign prostatic hyperplasia as well as androgenic alopecia (Nickel et al., 2008). In humans, Finasteride has a much higher affinity for 5αR2 than 5αR1, while dutasteride inhibits both isoenzymes; importantly, such inhibition is a nearly irreversible process, with a slow rate of dissociation and long-lasting effects in humans (Traish, 2020). In terms of clinical application in the treatment of benign prostatic hyperplasia, both of these drugs induce DHT suppression, which ultimately leads to the reduction of prostate volume and a general improvement of urinary symptoms. Compared to finasteride, dutasteride therapeutic effects seems to be more rapid and to result in a greater and long-term improvement of urinary retention (Nickel, 2004; Nickel et al., 2008).

In parallel with the therapeutic indications of 5αR inhibitors, the 5α reductase pathways, alongside its substrates and metabolites, is increasingly recognized as particularly relevant in diverse stress- and dopamine-related brain disorders. A specific disruption of 5αR enzymatic pathway, along with associated imbalances of NaS, has been consistently observed in patients with schizophrenia, Tourette's syndrome (TS), Post-Traumatic Stress Disorder (PTSD), and cannabis use disorders (Bortolato et al., 2022, 2022; Cai et al., 2018; Marx et al., 2006; Pineles et al., 2018; Rasmusson et al., 2006; Tomaselli and Vallée, 2019). Of note, these diseases are etiologically characterized by hyperdopaminergic states. In the next sections, we will present the most relevant preclinical and clinical evidence showing how targeting neurosteroidogenesis within the 5α, 3α pathway and/or exogenous administration of their associated NaS, can significantly modulate dopamine transmission in brain regions and circuitry strictly involved in these psychiatric conditions.

1.3. *The modulatory effects of 5α related NaS on dopamine system*

The mesolimbic dopamine system is central to modulating various processes across neurobehavioral domains, including decision-making, motivation, information and reward processing, and emotional responses (Salamone and Correa, 2012; Zald and Treadway, 2017). Consequently, dysfunction or dysregulation of the mesolimbic dopamine pathway is widely recognized as a key etiological factor in major psychiatric disorders such as addiction, mood disorders, and schizophrenia. The primary approach of marketed drugs for these disorders is to target this pathway in order to restore physiological dopamine balance and/or to regulate dopamine receptor signaling. Examples of currently used therapeutics that modulate dopamine system include dopamine receptor antagonists for schizophrenia and bipolar disorders, dopamine agonists for PD, dopamine releasers (i.e. amphetamine-like drugs) for ADHD, and dopamine reuptake inhibitors for depression. However, due to dopamine involvement in several physiological processes, directly targeting dopamine synaptic function, and/or single or multiple dopamine receptors often leads to undesirable, and sometimes severe, side effects. An alternative and promising approach may, therefore, involve an indirect neuromodulation of this system to potentially achieve similar neurobiological outcomes while minimizing adverse effects on behavioral regulation. From this standpoint, compelling evidence indicates that NaS play a modulatory role on midbrain dopamine system (Di Paolo, 1994; Sánchez et al., 2010). Among the subclasses of NaS, it is noteworthy that all the substrates and metabolites of the 5α reductase pathways, namely PREG, progesterone, 5α-DHP and AP, demonstrated disparate and multifold modulatory actions on dopamine transmission and signaling. For example, PREG administration has been shown to modulate dopamine release in the rodent PFC, thus suggesting a role in cognitive functions and a potential avenue in disorders where dopamine dysregulation is implicated. Consistent with this evidence, it dose-dependently rescues schizophrenia-like behavior phenotypes in dopamine transporter (DAT) knockout mice (Wong et al., 2012). Exogenous PREG administration significantly counteract a spectrum of hyperdopaminergic behavioral phenotypes due to deletion of DAT in the brain, including psychomotor agitation, stereotypy, and cognitive deficits in the prepulse inhibition (PPI) and object recognition tests (ORT) (Vallée et al., 2014; Wong et al., 2012). In partial agreement with these findings, the largest randomized clinical trials reported that exogenous PREG supplementation improved functional capacity in patients with schizophrenia compared to placebo, but failed to significantly improve cognitive symptoms (Marx et al., 2014). Activation of ventral tegmental area (VTA) dopaminergic neurons and an increase in dopamine extracellular levels in the NAc are hallmark effects of most drugs of abuse and have been implicated in drug addiction. Accordingly, Δ9-tetrahydrocannabinol (THC) elicits a robust increase in extracellular NAc dopamine levels alongside firing activity of VTA neurons. Remarkably, not only PREG dampens these neurochemical and electrophysiological outcomes, but also reverses the reinforcing effects assessed in an intravenous self-administration model, suggesting potential therapeutic applicability for cannabis intoxication and further dopamine-dependent addictive behaviors (Vallée et al., 2014).

By influencing the expression and the activity of dopamine receptors, progesterone also regulate dopamine function. At physiological doses, it can rapidly increase striatal dopamine release in rats of both sexes, and independently from estradiol actions (Di Paolo et al., 1986; Ringuet et al., 1994). However, at higher doses, the changes in dopaminergic signaling within the dorsal and ventral striatum are time-dependent, with rapid increases in dopamine release immediately after acute hormone administration followed by later inhibition (Dluzen and Ramirez, 1984; Yoest et al., 2018). Of interest, the fluctuations of progesterone (and estradiol) levels across the menstrual cycle differently affect cognitive performance by modifying baseline dopamine levels in the PFC (Hidalgo-Lopez and Pletzer, 2017). However, data regarding dopamine receptor expression in response to progesterone administration appear controversial, with no changes or time-dependent effects on expression of striatal dopaminergic D2 receptors (Fernández-Ruiz et al., 1989; Lévesque and Di Paolo, 1993; Paden et al., 1982; Saigusa et al., 1997). The direct metabolite of progesterone, 5α-DHP, has been less investigated in the context of dopamine regulation. However, previous evidence suggests that it may exert modulatory effects on dopamine transmission. For instance, a study by (Frye et al., 2006) demonstrated that 5α-DHP administration affects dopamine release in the NAc, implicating its involvement in reward-related behaviors mediated by the dopaminergic system.

AP is the 5αR-related NaS has received major attention with regard to its neuromodulatory effects on dopamine neurotransmission. The impact of AP on dopamine function in the rodent brain appears to exhibit narrow dose ranges and a hormetic dose response curves. For instance, at estimated physiological levels, AP enhances mesolimbic dopamine transmission and potentiates the dopamine response to morphine in the NAc, suggesting an important role in reward and motivation (Rougé-Pont et al., 2002). Consistent with these findings, AP facilitates reward-related behavior (Fish et al., 2014; Frye et al., 2011)

and reinstates ethanol-seeking behavior (Finn et al., 2008, 2004). AP also modulates the behavioral effects of D1 receptor activation (Frye et al., 2006) and affects the phosphorylation of DARPP-32 (Frye and Walf, 2010; Mani et al., 2000), a key molecule in dopamine D1 receptor signaling cascade (Scheggi et al., 2018; Svenningsson et al., 2004). Conversely, at supraphysiological concentrations (micromolar range), AP dose-dependently blocks hyperlocomotion and hyperactivity induced by amphetamine (Khisti et al., 2002), reduces sexual receptivity in female rats (Laconi and Cabrera, 2002), and produces place aversion (Beauchamp et al., 2000), akin to dopamine antagonists. Additionally, in vitro studies have shown that AP significantly decreases the amount of dopamine release in stimulated neurons, an effect attenuated by the $GABA_A$ antagonist bicuculline (Knight et al., 2012). Since AP preferentially activates extrasynaptic $GABA_A$ receptors, it may affect GABA tonic currents on VTA dopamine neurons, thereby inhibiting dopamine transmission (Vashchinkina et al., 2014). Consistent with this idea, AP administered intraperitoneally at escalating doses reduced evoked dopamine release in the NAc. This suggests that AP is able to blunt the phasic increase in NAc dopamine levels induced by electrical stimulation of VTA (Dornellas et al., 2020). Thus, collectively, these data support the notion that AP regulates mesolimbic dopamine transmission via specific $GABA_A$ receptor subtypes, in a dose-dependent manner. This interpretation is indeed strengthened by other studies showing that several $GABA_A$ agonists reduce dopaminergic transmission in the striatal regions (Brodnik et al., 2019; Smolders et al., 1995), and bicuculline, $GABA_A$ receptor antagonist, prevents dopamine increase induced by AP in stimulated striatal neurons (Knight et al., 2012).

The effects of AP on dopamine signaling also show a state-dependent modulation, especially in the context of stress response. Acting as a positive allosteric modulator of $GABA_A$ receptors, AP may regulate emotional behavior and exert anti-anxiety, anti-conflict and anti-nociceptive effects (Pinna et al., 2003). When subjected to acute stress paradigms, such as foot shock experiments, rodents exhibit increased dopamine release in several brain regions, including the PFC (Abercrombie et al., 1989; Deutch and Roth, 1990). Concomitantly, acute stress exposures triggers rapid increases in cortical and plasma concentrations of AP (Barbaccia et al., 1997, 1996; Cadeddu et al., 2022). Moreover, AP robustly reduces the extracellular concentration of dopamine in rat NAc and cerebral cortex, both at baseline and after its increase in response to stress (Motzo et al., 1996). Conversely, depletion of cortical AP enhances dopamine release induced by acute stress exposure (Dazzi et al., 2002), suggesting that AP contributes to the physiological regulation of basal and stress-induced dopamine release in the rat brain. AP influence extends to modulating dopaminergic neurotransmission under chronic stress conditions. For instance, in rats, the post-weaning isolation-rearing model of chronic stress elicits imbalances of AP and dopamine levels within the NAc and medial PFC, thus reflecting the complex interplay between AP signaling and chronic stress-induced neuroadaptations (Bortolato et al., 2011). This underscores the intricate and multifaceted role of AP in shaping dopaminergic neurotransmission under both acute and chronic stress conditions, shedding light on its therapeutic potential in mitigating stress-related neuropsychiatric disorders.

Typically, AP is posited to promote resilience and mitigate adverse outcomes of acute and short-term acute stress. However, its prolonged level elevation beyond physiological norms shifts brain homeostasis towards pathological behavioral changes. Consequently, numerous preclinical and clinical investigations indicate that exogenous or intracerebral AP infusions lead to impairments across multiple neurobehavioral domains, including cognition, impulse control and information processing. For instance, AP elicits learning and memory deficits in various cognitive tasks in rodents (Johansson et al., 2002; Johansson et al., 2016; Cushman et al., 2011; Rabinowitz et al., 2014); in healthy women, an acute AP administration with a dose inducing tenfold plasma endogenous concentrations produces a small but significant deterioration of episodic memory scores without interfering with semantic or working memory (Kask et al., 2008). Similar cognitive deficits are observed following the administration of the further PAM-steroid, THDOC (Schwabe et al., 2007). In light of this evidence, human conditions characterized by intrinsic supraphysiological AP levels, namely hepatic encephalopathy (Montagnese et al., 2021; Riggio et al., 2011) and primary biliary cholangitis (Wetten et al., 2022), show impairments in cognitive functions. Additionally, AP exposures may also exacerbate preexisting behavioral phenotypes with relevance to neurological and psychiatric conditions. Continuous AP exposures through implanted Alzet® osmotic pump impairs learning and memory in mice models of Alzheimer's disease (Bengtsson et al., 2013, 2012). Moreover, in relation to stress exposure, AP may contribute to maladaptive processes in vulnerable subjects. For example, AP dose-dependently exacerbates TS-like manifestations induced by stress in D1CT-7 mice, one of the best-characterized animal models of Tourette's syndrome; interestingly, the same AP doses failed to affect wild-type littermates (Mosher et al., 2017). Sleep deprivation, a further stressful situation, which is known to precipitate tic expression, produced sensorimotor deficits in rats by enhancing AP biosynthesis in the PFC (Cadeddu et al., 2023, 2022). Consistently, the exogenous administration of AP worsens sensorimotor gating function deficits in sleep deprived rats (Frau et al., 2017). Notably, the administration of finasteride reversed both the TS- and psychotic-like manifestations of D1CT-7 mice and sleep deprived rats, respectively, by recovering AP physiological levels. Accordingly, PAM-steroids alike AP produce paradoxical responses, characterized by irritability, aggression, and dysphoria, similar to those observed in premenstrual syndrome during the luteal phase and in treatments involving post-menopausal hormone replacement therapy (Bäckström et al., 2015).

1.4. 5α reductase enzyme as a therapeutic target for hyperdopaminergic phenotypes

As previously discussed, 5αR acts as a crucial enzyme in the biosynthesis of NaS, which exhibit distinctive modulatory effects on the dopaminergic system. Extensive literature indicates that pharmacological or environmental modulation of this enzyme leads to substantial alterations in its related neuroactive substrates and metabolites across cortical and limbic brain regions. Consequently, these alterations give rise to a diverse array of effects on emotional and cognitive regulation, as observed in both rodent models and humans. Numerous preclinical studies have demonstrated that, under baseline conditions, the selective inhibition of 5αR results in two distinct neurochemical outcomes in the brain: (i) depletion of its products, especially AP; (ii) elevation of its substrates, primarily progesterone and PREG (Bortolato et al., 2011; Dazzi et al., 2002; Frau et al., 2016; Griffin and Mellon, 1999). Finasteride and dutasteride – two clinically approved drugs for the treatment of benign prostatic hyperplasia and androgenetic alopecia – are the most used 5αR inhibitors in the preclinical setting to manipulate the levels of these NaS and explore their effects on brain function and behavior.

In light of this, our research group focused on investigating the impact of the pharmacological modulation of 5αR pathway in animal models relevant to major psychiatric disorders characterized by dysregulation of NaS and dopamine system. Initially, we evaluated the effect of 5αR inhibitors in ameliorating abnormal behaviors induced by psychotomimetic agents, including the dopaminergic agonists apomorphine and d-amphetamine, as well as the NMDA receptor antagonist dizocilpine. Notably, the antipsychotic-like properties of 5αR blockade were assessed on behavioral phenotypes isomorphic to preattentional, motor, and cognitive abnormalities observed in schizophrenia and other psychiatric disorders (Geyer et al., 2001), whose symptoms are mitigated by antipsychotic drugs (Geyer et al., 2001; Hoffman et al., 1993). Alongside hyperlocomotion and stereotyped behavior — two well-established assays for measuring hyperdopaminergic-relevant phenotypes with high predictive validity for typical and atypical antipsychotics — we focused our investigations on the PPI of the acoustic startle reflex and its deficits

mediated by dopamine agonists and NMDA antagonists (Mansbach and Geyer, 1989). PPI refers to the normal reduction in startle amplitude occurring when a startling stimulus is preceded by a weaker prepulse and serves as a measure of preattentional sensorimotor gating. This endophenotype has been extensively used to mimic the documented gating deficits observed in schizophrenia and other dopamine-dependent psychiatric conditions (Swerdlow et al., 1994). The high face, construct and predictive validity of PPI for these disorders is underscored by the observation that administration of major psychotomimetic agents significantly disrupts the PPI index in both animals and humans, and in a manner sensitive to typical and atypical antipsychotic drugs (Geyer et al., 2001). Moreover, aside from schizophrenia, the loss of PPI has also been documented in other neuropsychiatric disorders associated with dopamine dysregulation, such as mania (Perry et al., 2001), TS (Swerdlow et al., 2001), thereby revealing itself as a transdiagnostic endophenotype for gating- and dopamine-dependent disorders (Frau and Melis, 2023; Geyer, 2006).

Our initial findings show that 5αR inhibitors efficiently prevented PPI deficits along with other dopamine-relevant behavioral alterations (Bortolato et al., 2008). Importantly, their antidopaminergic properties were not associated with extrapyramidal symptoms typically exerted by neuroleptic drugs, even at the highest doses tested (Bortolato et al., 2008). Moreover, the rapid onset of all the behavioral effects observed after acute finasteride administration and other 5αR inhibitors, suggests that the neuromodulatory actions of NaS of the dopamine system likely operate through non-genomic signaling.

In our endeavor to elucidate how finasteride modulates the dopamine system, we uncovered that the therapeutic effects prompted by 5αR inhibition entail the involvement of two key target areas of the mesolimbic and mesocortical dopaminergic pathways, the NAc and the medial PFC (Devoto et al., 2012). These brain regions are prominent in the dopaminergic regulation of sensorimotor gating, and are implicated in the pathophysiology of schizophrenia and various other psychiatric disorders. Moreover, the influence of 5αR inhibition on the dopaminergic regulation of sensorimotor gating function exhibits regional specificity, as evidenced by the absence of contribution from other forebrain regions, including the dorsal caudate, basolateral amygdala, and ventral hippocampus (Devoto et al., 2012; Frau et al., 2023). While our prior investigations suggest that systemic administration of finasteride leads to heightened dopamine levels in the Nac and medial PFC (Bortolato et al., 2011), our subsequent research revealed that its intracerebral infusion failed to elicit any alterations in extracellular dopamine contents within these regions (Devoto et al., 2012; Frau et al., 2016). These findings suggest that the antipsychotic-like effects of finasteride primarily stem from postsynaptic mechanisms and are functionally distinct from time-dependent fluctuations in cortical and striatal dopamine levels that follow systemic administration of 5αR inhibitors.

We next investigated which receptor(s) might be involved in the antipsychotic-like effects of 5αR inhibitors. To address this question, we employed different strains and rodent species known to be susceptible to the PPI-disrupting effects of selective D1, D2, and D3 dopaminergic agonists, such as C57BL/6 mice and Long Evans rats. Across two consecutive studies, we discerned that the antidopaminergic properties of finasteride are mediated through the negative modulation of D1 and D3 receptors, while D2 receptors remained unaffected (Frau et al., 2016, 2013). Considering that 5αR inhibitors do not directly bind to dopamine receptors and the observed postsynaptic mechanism of action of finasteride on PPI regulation (Devoto et al., 2012), it is conceivable that the NaS changes produced by 5αR inhibition may interfere with downstream signaling pathways associated with D1 and D3 receptors. While the quantification of brain regional changes in 5αR-related NaS accompanying the antipsychotic-like effects of finasteride was not conducted across the aforementioned investigations, our recent steroidomic analysis show that the PPI-disrupting effect induced by selective D1 receptor agonist was concomitant with elevated levels of progesterone and some of its metabolites in the medial PFC (Frau et al., 2023). This finding suggests that the D1 receptor activation results in an upsurge of progesterone levels that may ultimately lead to increased AP concentrations, possibly attributable to heightened 5αR expression and/or activity. Notably, in the same study we showed that medial PFC levels of AP are necessary and sufficient to confer sensitivity to the PPI-disruptive effects of D1 receptor agonists in rodents (Frau et al., 2023; Cadeddu et al., 2022). Consistent with our results, other groups have shown that progesterone and AP modulate the behavioral effects of D1 receptor activation (Apostolakis et al., 1996; Frye et al., 2006; Petralia and Frye, 2006) as well as its signaling, such as the phosphorylation of DARPP-32 (Frye and Walf, 2010; Mani et al., 2000), a key molecule in the D1 receptor downstream cascade (Svenningsson et al., 2004). Moreover, both NaS affect σ1 receptors, a protein chaperone known to enhance D1 receptor signaling (Fu et al., 2010) and to form heteromers with this receptor in the brain (Navarro et al., 2010). This aligns with findings suggesting that D1/D3 receptor blockers might prove useful in treating TS and schizophrenia, respectively (Gilbert et al., 2014; Sokoloff et al., 2013). Noteworthy, our preclinical findings have been substantiated by clinical investigations showing how finasteride exerted beneficial properties in patients suffering from these psychiatric conditions (see next sections) (Bortolato et al., 2007; Koethe et al., 2008; Muroni et al., 2011).

1.5. *Targeting 5α reductase pathway for L-DOPA-induced dyskinesia*

Prompted by our experimental results on the antidopaminergic effects elicited by 5αR inhibitors in psychotic-like phenotypes, we hypothesized similar therapeutic efficacy against L-DOPA-induced dyskinesias (LID), as this condition is also characterized by dopamine receptor signaling disruption. Indeed, LID is a serious side effect of chronic L-DOPA administration, which limits therapeutic efficacy and management of motor symptoms in advanced PD patients. Given that amantadine, the only current treatment option, exhibits limited efficacy and is associated with side effects, there is an urgent need to identify novel and more effective drugs. This aberrant motor behavior can be readily reproduced and studied in preclinical models of PD upon chronic L-DOPA treatment, which is associated with an increased phosphorylation of striatal cell modulators downstream to D1 receptors, such as pERK1/2 and pDARPP32 (Pavón et al., 2006; Santini et al., 2007)

In line with our hypothesis, in a first study we found that finasteride dampened the development of LID in 6-OHDA-lesioned male rats as well as in dyskinetic animals upon L-DOPA administration. The latter effect was also extended to female animals, albeit only with the higher tested dose. Most importantly, this effect was achieved without compromising the therapeutic efficacy of L-DOPA in ameliorating motor disability (Frau et al., 2017). The latter finding is pivotal for the translation of preclinical results to clinical applications. The antidyskinetic effect appeared to be mediated through post-synaptic neurons, as evidenced by finasteride ability to reduce dyskinesias induced by direct dopamine receptor agonists, thereby ruling out modulatory effects on L-DOPA-derived dopamine release (Frau et al., 2017).

In a subsequent study, we compared the antidyskinetic effect of finasteride with the one of its analog, namely dutasteride. This 5αR inhibitor was found as effective as finasteride but at half of the dose, again without reduction of the therapeutic efficacy of L-DOPA on rescuing of motor deficits induced by the dopaminergic denervation (Fanni et al., 2019). Remarkably, the effect of 5αR inhibitors was accompanied by the normalization of striatal signaling molecules that are upregulated upon chronic L-DOPA, such as pERK1/2, pDARPP-32, and $G\alpha_{olf.}$

Whereas the precise mechanism by which 5αR inhibitors exerts their antidyskinetic effect is not known, it may involve inhibition of D1-D3 receptor interaction. Indeed, chronic L-DOPA has been shown to produce upregulation of striatal D3 receptors that are otherwise expressed at low levels in physiological conditions (Aubert et al., 2005; Bézard et al., 2003; Bordet et al., 2000; Guillin et al., 2001). This event may yield to the formation of heteromeric complexes that display different

functional properties compared to homomeric receptors. In fact, it has been hypothesized that the bond of D3R to D1R prevents D1R internalization and potentiates its signaling cascade at striatal neurons (Fiorentini et al., 2008; Marcellino et al., 2008; Solís et al., 2017). According to this scenario, the antidyskinetic effect of 5αR inhibitors was paralleled by decreased D1-D3 receptor coimmunoprecipitation in striatal homogenates. Of note, the ability of 5αR inhibitors to interfere with D1R-D3R heteromer formation was restricted to the lesioned striatum, suggesting that dopamine depletion and pulsatile stimulation of its receptors are mandatory for dysregulated D1-D3 receptor interaction and prevention of thereof by dutasteride or finasteride. Thus, it is conceivable to posit that these heteromeric complexes primarily contribute to the upregulation of striatal signaling molecules, such as pERK1/2, pDARPP-32, and Gαolf, thereby exacerbating both the behavioral and biochemical outcomes in response to dopaminomimetics.

In the effort to advance our understanding of the mechanisms underlying the antidyskinetic effects observed with finasteride and dutasteride, we investigated which NaS may be responsible for the antidyskinetic effect of 5αR inhibitors. Interestingly, striatal PREG levels were reported to be specifically decreased following 6-OHDA lesion (Melcangi et al., 2012). Conversely, as mentioned earlier, pharmacological 5αR inhibition results in increased levels of its NaS substrates, especially PREG (Frau et al., 2017). Therefore, we explored whether direct administrations of PREG to 6-OHDA-lesioned male rats might impact response to L-DOPA (Corsi et al., 2023). Results showed that concomitant treatment with PREG and L-DOPA reduced LID in a dose-dependent manner, akin to the effects observed with dutasteride. Once again, the therapeutic effect of L-DOPA was not affected by either treatment. Moreover, similar to dutasteride, the effect of PREG was associated with significant reduction of expression of dyskinesia markers expression, including pERK1/2, pDARPP-32, as well as D1-D3 receptors coimmunoprecipitation (Corsi et al., 2023). Interestingly, D1-D3 receptor coimmunoprecipitates showed a significant correlation with striatal BDNF levels. In fact, previous work has shown that L-DOPA treatment can induce BDNF expression, which in turn, can exacerbate maladaptive responses to L-DOPA (Guillin et al., 2001; Rylander et al., 2010). Accordingly, we found that striatal BDNF overexpression achieved through the delivery of a viral vector encoding the human BDNF gene, precipitated dyskinesia induced by both L-DOPA and direct D1 receptor agonists in 6-OHDA-lesioned rats (Scheggi et al., 2020; Tronci et al., 2017). Of note, this effect was paralleled by increased D1-D3 receptor coimmunoprecipitation. Indeed, previous work has shown that D3 receptor expression is under control of the BDNF gene (Guillin et al., 2001). Thus, by increasing D3 expression, BDNF would promote formation of dopamine receptor heterodimers, thus altering D1 receptor signaling cascade (Corsi et al., 2023). It is worth noting that, in our study, BDNF overexpression *per se* did not modify the levels of striatal D1–D3 receptor complexes, despite the increased availability of D3 receptors. By contrast, D1 receptor activation appeared essential to trigger heteromer formation, possibly by recruiting D3 receptors to the synaptic membrane (Scheggi et al., 2020). Taken together, these results suggest that PREG effect may be mediated through inhibition of L-DOPA-induced BDNF upregulation, prevention and D1-D3 heterodimer formation and consequent inhibition of the phosphorylation of key striatal signaling molecules that drive the exaggerated motor response to L-DOPA.

Although multiple NaS could potentially contribute to the antidyskinetic effect of PREG and 5αR inhibitors, a specific increase of striatal PREG levels was observed following its exogenous administration, with no changes in the levels of other NaS. Similarly, elevated PREG levels were measured after 5αR inhibitors treatment (Frau et al., 2015; Corsi et al., 2023). Although other steroids were not investigated in these studies, they could potentially contribute to the observed antidyskinetic effect through parallel mechanisms, such as mitigating inflammation, as demonstrated by corticosterone administration (Barnum et al., 2008). A direct involvement of progesterone appears to be unlikely since its acute administration has been shown to increase dopamine release (Di Paolo et al., 1986), and no improvement of dyskinesia was observed in non-human primates lesioned with MPTP (Gomez-Mancilla and Bédard, 1992) or in clinical settings (Nicoletti et al., 2007). On the other hand, medroxyprogesterone in combination with other estrogens significantly improved dyskinesia in post-menopausal women (Nicoletti et al., 2007).

Despite additional studies are required to deepen our understanding of the contribution of multiple NaS to the pathophysiology of LID, the existing evidence strongly suggests the ability of these mediators to interfere with the maladaptive response to chronic L-DOPA after dopaminergic denervation.

1.6. Targeting 5α reductase pathway in probability-discounting phenotypes produced by pramipexole

Neurosteroid modulation could be also a promising treatment option for iatrogenic complications caused by dopaminergic agonists, particularly gambling disorder (GD). Over the last few decades GD has become a serious recognized complication in PD, occurring in approximately 6 % of PD patients upon dopamine agonist medications. In particular, the dopaminergic agonists pramipexole and ropinirole, used in the therapy of PD, are associated with increased risk of developing hypersexuality, compulsive shopping, binge eating and pathologic gambling as adverse effects (Dodd et al., 2005; Weintraub et al., 2010; Weintraub and Mamikonyan, 2019). Despite growing attention and alarm on the impact of gambling on public health, therapeutic options are still inadequate (gradual reductions in dopaminergic agonists, antidepressants, antipsychotic medications, see (Jeon and Bortolato, 2020) and (Debove et al., 2024) for a detailed description) and efforts are urgently needed to clarify pathway strategies for high quality evidence.

In order to study the neurobiological mechanisms underlying GD, translational constructs have been developed to investigate impulsivity and risky decision making. By using these tasks, acute pramipexole was able to increase rat impulsive behavior (Madden et al., 2010) and to impair the ability to discriminate between advantageous and disadvantageous options (Pes et al., 2017).

To specifically model what happens in a subset of PD patients treated with pramipexole, our group has developed a model of iatrogenic gambling: using low doses of reserpine to mimic the dopamine deficit typical of PD without inducing motor alterations, pramipexole did not simply increase impulsive behavior but specifically reduced the ability to differentiate between distinct reward-associated choices (Orrù et al., 2020). Dysfunctional activation of reward and reinforcement systems in the brain, and possibly in dopamine function, has been proposed as one of the neurobiological underpinnings of GD (Balodis and Potenza, 2020). Neuroimaging studies have indeed showed a prominent involvement of frontal cortex and striatal regions (Hammes et al., 2019) and enhanced dopamine release in ventral striatum in PD patients with GD during the execution of gambling task (Steeves et al., 2009); reviewed by (Clark et al., 2019).

Thus, in searching novel therapies for GD, and consistently with the observation that the 5αR inhibitor finasteride is endowed with antidopaminergic effects on several different paradigms (as reviewed in Frau and Bortolato, 2019) and elicited anti-dyskinetic properties in rodent models of PD (Fanni et al., 2019; Frau et al., 2017), NaS modulation may have some efficacy in attenuating risky behavior. Regarding the possible efficacy of 5αR inhibitors in gambling disorder induced by dopamine agonists, the case report of Bortolato et al., 2012 is particularly remarkable. A 65-year old man with a history of PD received cabergoline or pramipexole in addition to his L-DOPA regimen and then developed gambling and compulsive habits, rapidly escalating. Since the patient was then diagnosed with benign prostatic hyperplasia, he was administered with finasteride and reported a subsequent attenuation of gambling behaviors and urge to play (Bortolato et al., 2012). However,

when the patient was surgically exposed to a prostatectomy and finasteride was discontinued, the patient within 3 weeks resumed his gambling habits; interestingly, when finasteride was reinstated, gambling habits were attenuated within 2 weeks (Bortolato et al., 2012). This case report led us to hypothesize that 5αR inhibitors may effectively attenuate impulsivity, risk taking behavior and delay discounting, which are a common feature of behavioral addiction and predict gambling severity (Ciccarelli et al., 2020). In line with data of the case report, our group has demonstrated that in the reserpine-pramipexole model of pathological gambling, finasteride countered the elevation in probability-discounting (Floris et al., 2022). Several studies suggest that the pathological over-activation of reward dopaminergic system may be one of the potential mechanisms for dopamine agonists/modulators to induce GD, leading to a condition of sensitization of striatal circuits with abnormal activation of dopamine D2/D3 receptors, particularly in the NAc (Barrus and Winstanley, 2016; Murray et al., 1994; Steeves et al., 2009). Our studies suggest that finasteride contrasts the D3-upregulation in the NAc induced by pramipexole (Floris et al., 2022). It is possible that finasteride, reducing the biosynthesis of AP and inducing an accumulation of steroid precursors like PREG and progesterone (Frau et al., 2017, 2015) or dehydroepiandrosterone (Bosse et al., 2021) change mRNA levels of dopamine of D2/D3 receptors (Purves--Tyson et al., 2014) or dysregulate the intracellular trafficking of D3 receptors (Laurine et al., 2003; Murakami et al., 2000). It is also worth noting that finasteride may reduce the reactivity to incentive stimuli that play a central role in the neurobiology of addiction and substance abuse disorders. Indeed, finasteride reduces the response to both stressful and rewarding stimuli (Godar et al., 2019) and the self-administration of different opioids like morphine and fentanyl without affecting their antinociceptive properties (Bosse et al., 2021), suggesting that it may be useful in different conditions characterized by compulsive and maladaptive features comparable to drug addiction.

1.7. Effects of pregnenolone (PREG) on the hyperdopaminergic phenotypes produced by prenatal cannabis exposure

Exposure to environmental risk factors during crucial periods of brain development can profoundly affect multiple neuronal pathways governing cognitive, emotional, and behavioral functions, ultimately heightening the vulnerability to neuropsychiatric disorders. Within this context, growing preclinical and clinical literature suggests that prenatal cannabis exposure (PCE) is associated with a spectrum of neurobehavioral complications that could be ascribed to hyperdopaminergic etiologies. In fact, longitudinal studies investigating the impact of PCE on the major neurobehavioral domains in offspring have reported increased impulsivity, heightened incidence of risk-taking behaviors, and greater susceptibility to psychotic-like experiences and substance abuse (Corsi et al., 2019; Fine et al., 2019; Morris et al., 2011; Paul et al., 2021). Importantly, these investigations emphasize that such dopamine-related psychopathologies typically emerge during childhood and preadolescence, a period when the developing brain has not yet achieved complete maturation.

According to human studies, preadolescent PCE rat offspring displays a behavioral phenotype highly isomorphic with neurobehavioral disturbances observed in children. Moreover, rodent studies have uncovered two significant pieces of evidence yet to be extensively explored in humans: (i) the aberrant behavioral outcomes emerge only in males (Frau et al., 2019; Traccis et al., 2021); (ii) the psychopathological phenotypes of PCE offspring manifest only in response to an environmental challenge especially during preadolescence, namely THC –the major psychoactive component of cannabis– or acute stress exposure (Frau et al., 2019; Sagheddu et al., 2021; Traccis et al., 2021).

Thus, PCE has emerged as a viable rodent model for exploring the well-established "two-hit" hypothesis of mental illness. According to this conceptualization, an environmental insult acting as a "first hit," disrupts neurodevelopment thereby leading to increased susceptibility to a "second hit" later in life, which ultimately triggers the manifestation of psychiatric symptoms (Frau and Melis, 2023; Mandy and Nyirenda, 2018). In this framework, the sustained and supraphysiological activation of the endocannabinoid signaling during intrauterine life biases the neurodevelopmental trajectories that are under its intricate regulatory control. Importantly, among these neurodevelopmental pathways, the endocannabinoid system exhibits a critical tropism for dopaminergic structures and circuits within the mesocorticolimbic system, which are relevant to emotional and cognitive processes (Harkany et al., 2007; Hurd et al., 2019)

Consequently, one of the neurobiological consequences of PCE-dependent disruption of endocannabinoid signaling is the impairments of mesolimbic dopamine signaling and the increased susceptibility to aberrant dopamine-relevant behavioral phenotypes. Indeed, the psychopathological phenotypes of preadolescent PCE progeny are associated with heightened excitability of VTA dopamine neurons alongside larger THC-induced dopamine release in the ventral striatum (Frau et al., 2019; Luján et al., 2024). Additionally, PCE disrupts the excitatory/inhibitory balance onto VTA dopamine cells, and elicits a polarity shift at excitatory synapses, from long-term depression to long-term potentiation (Frau et al., 2019). Aligned with clinical observations indicating the onset of neuropsychiatric symptoms as early as infancy in maternally exposed offspring, it is noteworthy that PCE rats manifest sensorimotor gating deficits, and paradoxically exaggerated locomotor responses only upon exposures to acute THC challenge (or stress) during the preadolescence period (Frau et al., 2019; Sagheddu et al., 2021). Notably, PCE female offspring do not exhibit either spontaneous or THC-induced psychopathological phenotypes, but rather adaptive coping strategies to acute stress (Traccis et al., 2021), which are most likely implicated in the protection from stress-induced PPI deficits (M. Melis, personal communication). Hence, the biological variable sex may serve as a protective factor against harmful environmental insults across neurodevelopment.

The (endo)phenotype unveiled by PCE is thus instrumental for exploring potential therapeutic tools aimed at preventing the transition of individual psychiatric susceptibility into late-onset mental disease. As abovementioned, PREG has promising actions on a number of behavioral manifestations associated to aberrant hyperdopaminergic signaling in humans and rodent models. Remarkably, PREG also rescues psychotic-like states in rodents through an endogenous allosteric negative modulation of the CB1 receptor (Vallée, 2016; Vallée et al., 2014). Given these findings, we hypothesized that it could mitigate PCE-induced alterations in the properties of mesolimbic dopamine neurons and associated behavioral readouts. Thus, we repeatedly administered PREG to PCE offspring and conducted a meso- to macroscale analysis at least 24 after the final administration, in order to ensure a complete clearance of PREG from the body (Frau et al., 2019). Notably, PREG reversed both the intrinsic and synaptic hyperactive properties of dopamine neurons as well as their aberrant plasticity at excitatory synapses. It normalized the physiological responsiveness of mesolimbic transmission to acute THC administration and prevented THC-induced deficits in PPI. Additionally, PREG rescued the deterioration of PPI induced by acute stress in male PCE progeny (M. Melis, personal communication). Importantly, these remarkable antidopaminergic effects were attributed solely to PREG and not to its downstream neuroactive metabolites (e.g., progesterone, 5α-DHP, AP), as pharmacological inhibition of the enzyme responsible for its metabolism, 3-β-hydroxysteroid dehydrogenase, failed to antagonize its protective effects (Frau et al., 2019).

While the molecular mechanisms underlying PREG effects on multiscale phenotypes altered by PCE remain largely unexplored, the existing literature suggests that its therapeutic properties may be attributed to interactions with multiple molecular targets. For instance, PREG binds to the sigma-1 (σ1) receptor, a chaperone predominantly found in the endoplasmic reticulum and highly expressed in dopaminergic regions. This receptor is notably present in midbrain

dopaminergic neurons, where it plays a role in modulating dopamine function and release. Despite some contradictory findings regarding the effects of σ1 receptor activation on the dopamine system, its ligands, including PREG, have demonstrated the ability to mitigate dysregulated dopamine signaling induced by psychostimulant drugs (Monnet and Maurice, 2006; Romieu et al., 2006, 2003). Accordingly, prolonged administration of supraphysiological amounts of PREG (500 mg/day) has been shown to decrease cravings triggered by both stress and cocaine cues in individuals diagnosed with cocaine use disorder (Milivojevic et al., 2022).

Beyond its biological targets, PREG levels and related metabolites have been found to be altered in patients with dopamine-relevant psychiatric conditions, including schizophrenia, mood disorders, and substance abuse. In two clinical trials investigating the adjunctive use of PREG in chronic schizophrenia patients, Marx et al., (2014), (2011), (2009) reported significant improvements in SANS scores (Scale for the Assessment of Negative Symptoms) when this neurosteroid was added to second-generation antipsychotics, compared to a placebo group. Subsequent research expanded these findings by further assessing schizophrenia symptoms in a larger patient cohort, under two different doses of PREG (low and high dose) added to the same antipsychotic medications. The low dose of PREG, but not the high dose, significantly reduced positive and extrapyramidal symptoms, as well as improved attention and working memory performance. Overall, PREG supplementation was well tolerated, with circulating levels of this neurosteroid significantly elevated in treated patients compared to their placebo counterparts (Ritsner, 2010).

Moreover, the prototypical antipsychotic clozapine has been found to markedly elevate PREG levels both in schizophrenia patients and rodent models, thus corroborating the involvement of this neurosteroid in the neurobiology of schizophrenia and the response to treatment. Accordingly, an increase in PREG/pregnanolone ratio has also been found in a cohort of bipolar depressed individuals with a history of cannabis use disorders, and PREG supplementation results in higher rates of depression remission compared to placebo. While there is currently no study documenting changes in PREG levels in individuals exposed to cannabis during pregnancy, it is significant to emphasize that animal models strongly suggest the potential therapeutic role of this neurosteroid in mitigating the negative impact of PCE (first hit) on dopamine system function. As such, it may contribute to fostering resilience against "second hits," such as acute exposure to THC or stress, which often lead to the development of dopamine-dependent psychiatric disorders.

1.8. Clinical relevance and limitations of 5αR-related NaS in managing hyperdopaminergic-associated brain disorders

The recent approval of the synthetic analogue of AP, brexanolone, for the treatment of postpartum depression (PPD) has sparked renewed interest and momentum in the field of NaS, underscoring their clinical relevance and expanding their potential applications for psychiatric conditions. Marketed under the brand name ZULRESSO®, brexanolone stands as the first FDA-approved drug for PPD, offering a novel treatment option for women who do not respond adequately to conventional therapeutic interventions. Brexanolone exhaustively exemplifies both the risks and opportunities associated with NaS-based therapies in the clinical realm, as well as the need for careful consideration to attain optimal safety and efficacy profiles through this therapeutic strategy. For instance, brexanolone formulation requires intravenous administration over an extended period, typically ranging from approximately 60 to 90 hours, necessitating hospital admission and continuous patient monitoring to ensure the safe and effective delivery of the infusion. However, the desired rapid and enduring antidepressant properties of brexanolone are offset by its adverse effects, which include sedation, mental alterations, and the potential for loss of consciousness. Moreover, its administration may impact renal function, rendering it contraindicated in patients with severe renal disease. Additionally, the cost of brexanolone treatment in the US may be prohibitively expensive, thus limiting access to this therapy for many individuals.

In response to these challenges, the development of a further FDA-approved drug in 2023, namely zuranolone, has been pursued. Zuranolone, an analogue drug built upon an orally available formulation, offers similar rapid antidepressant effects and longer duration of efficacy compared to brexanolone (30 days vs. up to 45 days) (Nashwan et al., 2024). Notably, zuranolone demonstrates superior efficacy, a more favorable safety profile, and fewer side effects compared to brexanolone, indicating that the oral administration route for NaS may maintain an optimal pharmacokinetic profile and therapeutic efficacy (Clayton et al., 2024; Deligiannidis et al., 2021). The dosing regimen of zuranolone involves a single daily oral dose, eliminating the need for 60 hours of infusions and hospital admission, thereby reducing patient non-adherence to treatment.

The rapid mechanisms of action of brexanolone and zuranolone align with those highlighted in this review regarding 5αR-related NaS, thereby strongly suggesting that the exogenous administration of this class of NaS readily passes the BBB and immediately affects neuronal signaling. As mentioned earlier, the 5αR-associated NaS AP and PREG exert negligible effects on canonical intracellular steroid receptors. However, the persisting effects observed in PDD patients under brexanolone and zuranolone treatment, well beyond the presence of these drugs in the brain, cannot rule out the contribution of genomic actions. Alternatively, the sustained activation of $GABA_A$ receptor may mediate enduring structural and functional changes in neuronal plasticity through that are not yet fully understood. Likewise, in the hyperdopaminergic model of PCE, PREG rescues synaptic plasticity, mitigates deficits in dopamine neuron activity and restores behavioral phenotypes also 72 hours after the last administration, highlighting its potential to reprogram the mesolimbic dopamine system influenced by in utero THC exposure. Therefore, their ability to modulate dopaminergic signaling, along with their broader neuroprotective and neuroplastic effects, suggests they could have a unique multifaceted impact on psychiatric disorders characterized by acute symptomatic manifestations alongside underlying chronic pathophysiological processes (e.g. L-DOPA-induced dyskinesia in PD patients, tic manifestations in TS patients, and uncontrollable urges to gamble in impulse control disorders). However, further research is warranted to fully elucidate the mechanisms of action of this class of NaS to maximize their clinical application in treating dopamine-dependent psychiatric conditions.

The long-lasting effects shared by 5αR-related NaS may overcome their well-known limitations stemming from poor bioavailability, short biological half-life, and rapid in vivo metabolism, which historically have hindered their clinical application. For instance, upon oral administration of PREG, high levels of this NaS can be detected in human samples, along with multiple related metabolites, including AP and its sulfated derivatives (Brown et al., 2014; Marx et al., 2014, 2009; Sripada et al., 2013). To address these limitations, synthetic PREG analogues have been developed with improved bioavailability and safer profiles compared to their parent molecule. One such analogue is pregnenolone-methyl-ether (PME, 3β-methoxy-pregnenolone), which features a methylation at position 3 conferring resistance to conversion back to PREG or into other steroids and metabolites, both peripherally and centrally (Bianchi and Baulieu, 2012). Notably, PME readily crosses the rodent BBB following a single injection. Intriguingly, this compound seems to not have off-targets as it does not bind to several different neurotransmitter receptors (including NMDA and GABA-A) or transporters. Instead, it exerts biological activity on MAP2 and CLIP170, microtubule-associated proteins pivotal in microtubule dynamics and neuronal plasticity. Moreover, other PREG analogues have been developed in recent years. For instance, C3-C17 PREG analogs acting as CB1 signaling-specific inhibitors have been developed by INSERM and *Aelis Farma Biotech* (patent n. WO2014083068 A1) and are currently under investigation for CB1-related disorders (Haney et al., 2023), and for

other pathological conditions associated with aberrant endocannabinoid signaling (Vallée, 2016).

As previously discussed, a complementary approach to modify NaS signaling in the brain is offered by pharmacological modulation of the enzymatic machinery responsible for their synthesis and metabolism. Within the PREG to AP pathway, three critical enzymes, 3α- and 3β-HSD and 5αR, can be targeted by indomethacin and trilostane, and finasteride (or dutasteride) respectively. While all these drugs efficiently inhibit their corresponding enzymes with various modes of competition against the endogenous substrate, only finasteride (and dutasteride) exhibit significant antidopaminergic activity in rodent models (Bortolato et al., 2008; Devoto et al., 2012; Frau et al., 2014, 2013). The robust preclinical findings obtained through these inhibitors were supported by human studies (Table 1). In the first investigation, finasteride demonstrated efficacy in reversing severe positive symptoms (delusions and florid hallucinations) and negative symptoms, as well as cognitive deficits in a male patient with chronic schizophrenia who did not respond to standard antipsychotic therapies (Koethe et al., 2008). Importantly, finasteride did not induce significant adverse effects, and upon discontinuation of the medication, the patient experienced a recurrence of psychotic symptoms, prompting him to request continuation of finasteride regimen (Nickel et al., 2008). However, placebo-controlled trials with adequate sample sizes are necessary to fully assess the potential therapeutic value of finasteride in patients with schizophrenia. Given the role of androgens and AP in the pathophysiology and clinical course of TS, 5αR inhibitors might provide a therapeutic tool for this condition. Moreover, excess of dopamine in the striatum is thought to disrupt thalamo-cortical circuits in TS, resulting in physical and vocal tics that significantly affect patients' life quality (Branca and Bortolato, 2024). Interestingly, tic disorders are more predominant in males and exacerbated by external stressors, strongly suggesting the involvement of 5αR-related NaS in their etiology. Moreover, dopamine agonists worsen tics, while dopaminergic antagonists dampen their severity (Sandor, 2003), especially through D1 receptor blockade (Gilbert et al., 2003). Considering these premises, finasteride was tested in adult male patients with TS. In two subsequent studies (Bortolato et al., 2007; Muroni et al., 2011), the administration of 5 mg/day of finasteride resulted in significant reductions of tic severity, as assessed by the Yale Tic Severity Scale. Importantly, finasteride showed limited side effects and good tolerability. Similar to what observed with schizophrenia patients, discontinuation of finasteride led to dramatic exacerbation of symptoms, which was mitigated by reinstating the 5αR inhibitor (Bortolato et al., 2013).

In spite of the limited side effects and favorable tolerability profile of finasteride, clinical applicability of 5αR inhibitors remains restricted. For instance, it is not feasible to use a drug that significantly interferes with androgen biosynthesis in TS patients, most of whom are children. Accordingly, concerns about the risk of reduced libido and sexual dysfunction have been raised in subsets of adult individuals undergoing finasteride treatment (Traish et al., 2015a, 2015b). Usually, sexual adverse events in patients taking finasteride may resolve either with continued treatment or upon discontinuation of the medication. However, recent reports highlight cases where symptoms such as reduced libido, erectile dysfunction, and orgasmic dysfunction, as well as psychological issues like depression, anxiety, and suicidal thoughts, persist even after finasteride therapy cessation (Giatti et al., 2024; Irwig, 2012; Traish, 2020; Traish et al., 2014). These persistent symptoms have been collectively termed as postfinasteride syndrome. The increased recognition of these issues prompted regulatory agencies, including the FDA, to update the labeling of finasteride and to include both the risks of depression and persistent sexual dysfunction.

Consequently, to be considered viable therapeutic options for psychiatric disorders, it is imperative to thoroughly investigate the neurobiological mechanisms underlying the actions of finasteride and other 5αR inhibitors.

A very promising NaS-based therapeutic approach for mental disorders involves the use of GABAA receptor modulating steroid antagonists (GAMSA). Notably, GABAA receptor activating compounds, such as AP and its analogs, can induce paradoxical negative psychiatric effects in susceptible individuals. These adverse effects may result from increased sensitivity to AP and/or significant fluctuations in its levels under various physiological and pathological conditions, including the menstrual cycle, pregnancy, postpartum periods, and hepatic encephalopathy (Bäckström et al., 2015). For example, in premenstrual dysphoric disorder (PMDD), a subgroup of women exhibits a spectrum of psychiatric symptoms (irritability, depressed mood, aggression, and emotional lability) correlating with AP level rise following ovulation at the beginning of the luteal phase. The effects of AP can be specifically blocked by its isomer, isoallopregnanolone (Sepranolone; UC1010, 3β-OH-5α-pregnan-20-one), as this GAMSA does not interfere with the actions of endogenous GABA or other GABAA agonists, such as benzodiazepines and barbiturates (Lundgren et al., 2003). In two subsequent clinical trials, Sepranolone has shown promising results in reducing PMDD symptoms compared to placebo (Bäckström et al., 2021; Bixo et al., 2017), including improvements in mood symptoms, distress, irritability, and physical symptoms. Notably, the timing of administration appears to be crucial, as its efficacy is most pronounced when AP levels reach their peak in the brain. Therefore, since Sepranolone has demonstrated good safety and tolerability in women, GAMSA can be a potential alternative or a complementary medication to 5αR inhibitors for managing psychiatric disorders characterized by supraphysiological brain AP levels.

1.9. Conclusions: are NaS on the route to personalized neuropsychiatric therapy?

The growing interest in precision medicine strategies and the effort to integrate biological markers within the neuropsychiatric field reflects a fundamental shift in our approach to understanding and treating mental diseases. This shift stems from a deepening recognition of the intricate complexity and heterogeneity inherent in these conditions. As such, there is an urgent need to tailor treatments targeting unique (epi) genetic and neurobiological profiles of each individual. Presently, psychiatric diagnosis and treatment primarily rely on symptomatic presentation, often overlooking the underlying psychobiological mechanisms and the intricate interplay between genetic predispositions and environmental influences on the trajectory of these disorders.

To overcome these limitations, the National Institute of Mental Health has proposed a novel translational framework (Research Domain Criteria, RDoC) aimed at circumventing the challenges posed by symptom-based diagnostic classifications in neuropsychiatric disorders. This framework posits a complementary approach that integrates observable and measurable behavioral (endo)phenotypes within the functional domains of emotion and cognition, underpinned by related neurobiological mechanisms. In this context, some of the findings outlined herein collectively highlight how NaS associated with the 5αR pathway are particularly suited for addressing hyperactivity of the mesolimbic dopamine system (neurobiology) that typically manifests by information processing deficit, recently recognized as endophenotype of RDOC sensorimotor domain. Notably, impairments in sensorimotor gating are consistently observed across various psychiatric conditions underpinned by aberrant function of mesolimbic dopamine signaling. Moreover, insights from animal models suggest that both the neurobiological underpinnings and behavioral outcomes that characterize these disorders are influenced by environmental perturbations, emphasizing the need for a comprehensive understanding of the complex interplay among genetic, neurobiological, and environmental factors. Once again, the PCE animal model provides by maternal cannabis exposure unveils in offspring an endophenotype of sensory information processing deficits arising from hyperdopaminergic states—an intermediate phenotype that can be ameliorated through PREG administration during preadolescence.

Consequently, the integration of NaS into this framework is particularly intriguing due to their involvement in modulating neurobiological pathways implicated in major psychiatric conditions, and evidence suggesting that they may address specific endophenotypes associated with hyperactivity of the mesolimbic dopamine system might be promising. Nonetheless, while the potential of NaS in personalized therapy is exciting, it is noteworthy to acknowledge that further research is needed to understand their mechanisms of action, optimize treatment protocols, and establish their utility as complementary biomarkers for patient stratification and monitoring. Overcoming these challenges is paramount to fully utilize NaS in clinical practice with safety and effectiveness.

Search strategies

The present review employed two primary databases (PubMed and Elsevier Embase) to thoroughly investigate the most pertinent preclinical and clinical literature regarding the impact of NaS on dopamine-related neuropsychiatric disorders through the involvement of 5α reductase pathway. The systematic analysis of the international literature was conducted in accordance with PRISMA guidelines, with adaptations for preclinical investigations. The databases were used to search articles published between 1982 and 2024, using the following keywords: “neurosteroids”, “neuroactive steroids”, “allopregnanolone”, “progesterone”, “pregnenolone”, “pregnanolone”, “sulphated neurosteroids”, “sulphated neuroactive steroids”, “steroid-PAMs”, “GAMSA” AND “dopamine”, AND “rodents”, AND “mouse”, AND “rat” AND “human” AND “patient”. 239 were included in the present work, and duplicates and unrelated manuscripts were excluded.

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References

Abercrombie, E.D., Keefe, K.A., DiFrischia, D.S., Zigmond, M.J., 1989. Differential effect of stress on in vivo dopamine release in striatum, nucleus accumbens, and medial frontal cortex. J. Neurochem. 52, 1655–1658. https://doi.org/10.1111/j.1471-4159.1989.tb09224.x.

Adeosun, S.O., Hou, X., Jiao, Y., Zheng, B., Henry, S., Hill, R., He, Z., Pani, A., Kyle, P., Ou, X., Mosley, T., Farley, J.M., Stockmeier, C., Paul, I., Bigler, S., Brinton, R.D., Smeyne, R., Wang, J.M., 2012. Allopregnanolone reinstates tyrosine hydroxylase immunoreactive neurons and motor performance in an MPTP-lesioned mouse model of Parkinson’s disease. PLoS One 7, e50040. https://doi.org/10.1371/journal.pone.0050040.

Akk, G., Covey, D.F., Evers, A.S., Steinbach, J.H., Zorumski, C.F., Mennerick, S., 2007. Mechanisms of neurosteroid interactions with GABA(A) receptors. Pharmacol. Ther. 116, 35–57. https://doi.org/10.1016/j.pharmthera.2007.03.004.

Akwa, Y., Young, J., Kabbadj, K., Sancho, M.J., Zucman, D., Vourc’h, C., Jung-Testas, I., Hu, Z.Y., Le Goascogne, C., Jo, D.H., 1991. Neurosteroids: biosynthesis, metabolism and function of pregnenolone and dehydroepiandrosterone in the brain. J. Steroid Biochem. Mol. Biol. 40, 71–81. https://doi.org/10.1016/0960-0760(91)90169-6.

Almeida, F.B., Fonseca, A.R., Heidrich, N., Nin, M.S., Barros, H.M.T., 2018. The effect of intracerebroventricular allopregnanolone on depressive-like behaviors of rats selectively bred for high and low immobility in the forced swim test. Physiol. Behav. 194, 246–251. https://doi.org/10.1016/j.physbeh.2018.06.014.

Almeida, F.B., Pinna, G., Barros, H.M.T., 2021. The role of HPA axis and allopregnanolone on the neurobiology of major depressive disorders and PTSD. Int. J. Mol. Sci. 22, 5495. https://doi.org/10.3390/ijms22115495.

Anker, J.J., Holtz, N.A., Zlebnik, N., Carroll, M.E., 2009. Effects of allopregnanolone on the reinstatement of cocaine-seeking behavior in male and female rats. Psychopharmacol. (Berl.) 203, 63–72. https://doi.org/10.1007/s00213-008-1371-9.

Apostolakis, E.M., Garai, J., Fox, C., Smith, C.L., Watson, S.J., Clark, J.H., O’Malley, B. W., 1996. Dopaminergic regulation of progesterone receptors: brain D5 dopamine receptors mediate induction of lordosis by D1-like agonists in rats. J. Neurosci. 16, 4823–4834. https://doi.org/10.1523/JNEUROSCI.16-16-04823.1996.

Arnaud, A., Suthoff, E., Stenson, K., Werneburg, B., Hodgkins, P., Bonthapally, V., Jonas, J., Meyer, K., O’Day, K., 2021. Number Needed to Treat and Number Needed to Harm analysis of the zuranolone phase 2 clinical trial results in major depressive disorder. J. Affect Disord. 285, 112–119. https://doi.org/10.1016/j.jad.2021.02.027.

Aubert, I., Guigoni, C., Håkansson, K., Li, Q., Dovero, S., Barthe, N., Bioulac, B.H., Gross, C.E., Fisone, G., Bloch, B., Bezard, E., 2005. Increased D1 dopamine receptor signaling in levodopa-induced dyskinesia. Ann. Neurol. 57, 17–26. https://doi.org/10.1002/ana.20296.

Bäckström, T., Bixo, M., Strömberg, J., 2015. GABAA receptor-modulating steroids in relation to women’s behavioral health. Curr. Psychiatry Rep. 17, 92. https://doi.org/10.1007/s11920-015-0627-4.

Bäckström, T., Ekberg, K., Hirschberg, A.L., Bixo, M., Epperson, C.N., Briggs, P., Panay, N., O’Brien, S., 2021. A randomized, double-blind study on efficacy and safety of sepranolone in premenstrual dysphoric disorder. Psychoneuroendocrinology 133, 105426. https://doi.org/10.1016/j.psyneuen.2021.105426.

Balodis, I.M., Potenza, M.N., 2020. Common neurobiological and psychological underpinnings of gambling and substance-use disorders. Prog. Neuropsychopharmacol. Biol. Psychiatry 99, 109847. https://doi.org/10.1016/j.pnpbp.2019.109847.

Barbaccia, M.L., Roscetti, G., Bolacchi, F., Concas, A., Mostallino, M.C., Purdy, R.H., Biggio, G., 1996. Stress-induced increase in brain neuroactive steroids: antagonism by abecarnil. Pharm. Biochem Behav. 54, 205–210. https://doi.org/10.1016/0091-3057(95)02133-7.

Barbaccia, M.L., Roscetti, G., Trabucchi, M., Purdy, R.H., Mostallino, M.C., Concas, A., Biggio, G., 1997. The effects of inhibitors of GABAergic transmission and stress on brain and plasma allopregnanolone concentrations. Br. J. Pharmacol. 120, 1582–1588. https://doi.org/10.1038/sj.bjp.0701046.

Barbaccia, M.L., Serra, M., Purdy, R.H., Biggio, G., 2001. Stress and neuroactive steroids. Int. Rev. Neurobiol. 46 243–272. https://doi.org/10.1016/s0074-7742(01)46065-x.

Barnum, C.J., Eskow, K.L., Dupre, K., Blandino, P., Deak, T., Bishop, C., 2008. Exogenous corticosterone reduces L-DOPA-induced dyskinesia in the hemi-parkinsonian rat: role for interleukin-1beta. Neuroscience 156, 30–41. https://doi.org/10.1016/j.neuroscience.2008.07.016.

Barrus, M.M., Winstanley, C.A., 2016. Dopamine D3 receptors modulate the ability of win-paired cues to increase risky choice in a rat gambling task. J. Neurosci. 36, 785–794. https://doi.org/10.1523/JNEUROSCI.2225-15.2016.

Baulieu, E.E., 1998. Neurosteroids: a novel function of the brain. Psychoneuroendocrinology 23, 963–987. https://doi.org/10.1016/s0306-4530(98)00071-7.

Beauchamp, M.H., Ormerod, B.K., Jhamandas, K., Boegman, R.J., Beninger, R.J., 2000. Neurosteroids and reward: allopregnanolone produces a conditioned place aversion in rats. Pharm. Biochem. Behav. 67, 29–35. https://doi.org/10.1016/s0091-3057(00)00299-9.

Belelli, D., Lambert, J.J., 2005. Neurosteroids: endogenous regulators of the GABA(A) receptor. Nat. Rev. Neurosci. 6, 565–575. https://doi.org/10.1038/nrn1703.

Bengtsson, S.K., Johansson, M., Backstrom, T., Nitsch, R.M., Wang, M., 2013. Brief but chronic increase in allopregnanolone cause accelerated AD pathology differently in two mouse models. Curr. Alzheimer Res. 10, 38–47. https://doi.org/10.2174/1567205011310010006.

Bengtsson, S.K., Johansson, M., Bäckström, T., Wang, M., 2012. Chronic allopregnanolone treatment accelerates Alzheimer’s disease development in AβPP (Swe)PSEN1(ΔE9) mice. J. Alzheimers Dis. 31, 71–84. https://doi.org/10.3233/JAD-2012-120268.

Bézard, E., Ferry, S., Mach, U., Stark, H., Leriche, L., Boraud, T., Gross, C., Sokoloff, P., 2003. Attenuation of levodopa-induced dyskinesia by normalizing dopamine D3 receptor function. Nat. Med. 9, 762–767. https://doi.org/10.1038/nm875.

Bianchi, M., Baulieu, E.-E., 2012. 3β-Methoxy-pregnenolone (MAP4343) as an innovative therapeutic approach for depressive disorders. Proc. Natl. Acad. Sci. USA 109, 1713–1718. https://doi.org/10.1073/pnas.1121485109.

Biggio, G., Pisu, M.G., Biggio, F., Serra, M., 2014. Allopregnanolone modulation of HPA axis function in the adult rat. Psychopharmacol. (Berl.) 231, 3437–3444. https://doi.org/10.1007/s00213-014-3521-6.

Bitran, D., Hilvers, R.J., Kellogg, C.K., 1991. Anxiolytic effects of 3 alpha-hydroxy-5 alpha[beta]-pregnan-20-one: endogenous metabolites of progesterone that are active at the GABAA receptor. Brain Res. 561, 157–161. https://doi.org/10.1016/0006-8993(91)90761-j.

Bixo, M., Ekberg, K., Poromaa, I.S., Hirschberg, A.L., Jonasson, A.F., Andréen, L., Timby, E., Wulff, M., Ehrenborg, A., Bäckström, T., 2017. Treatment of premenstrual dysphoric disorder with the GABAA receptor modulating steroid antagonist Sepranolone (UC1010)-A randomized controlled trial. Psychoneuroendocrinology 80, 46–55. https://doi.org/10.1016/j.psyneuen.2017.02.031.

Bordet, R., Ridray, S., Schwartz, J.C., Sokoloff, P., 2000. Involvement of the direct striatonigral pathway in levodopa-induced sensitization in 6-hydroxydopamine-lesioned rats. Eur. J. Neurosci. 12, 2117–2123. https://doi.org/10.1046/j.1460-9568.2000.00089.x.

Bortolato, M., Cannas, A., Solla, P., Bini, V., Puligheddu, M., Marrosu, F., 2012. Finasteride attenuates pathological gambling in patients with Parkinson disease. J. Clin. Psychopharmacol. 32, 424–425. https://doi.org/10.1097/JCP.0b013e3182549c2a.

Bortolato, M., Coffey, B.J., Gabbay, V., Scheggi, S., 2022. Allopregnanolone: The missing link to explain the effects of stress on tic exacerbation? J. Neuroendocr. 34, e13022 https://doi.org/10.1111/jne.13022.

Bortolato, M., Devoto, P., Roncada, P., Frau, R., Flore, G., Saba, P., Pistritto, G., Soggiu, A., Pisanu, S., Zappala, A., Ristaldi, M.S., Tattoli, M., Cuomo, V., Marrosu, F., Barbaccia, M.L., 2011. Isolation rearing-induced reduction of brain 5α-reductase expression: relevance to dopaminergic impairments. Neuropharmacology 60, 1301–1308. https://doi.org/10.1016/j.neuropharm.2011.01.013.

Bortolato, M., Frau, R., Godar, S.C., Mosher, L.J., Paba, S., Marrosu, F., Devoto, P., 2013. The implication of neuroactive steroids in Tourette's syndrome pathogenesis: A role for 5α-reductase? J. Neuroendocr. 25, 1196–1208. https://doi.org/10.1111/jne.12066.

Bortolato, M., Frau, R., Orrù, M., Bourov, Y., Marrosu, F., Mereu, G., Devoto, P., Gessa, G. L., 2008. Antipsychotic-like properties of 5-alpha-reductase inhibitors. Neuropsychopharmacology 33, 3146–3156. https://doi.org/10.1038/npp.2008.39.

Bortolato, M., Muroni, A., Marrosu, F., 2007. Treatment of Tourette's syndrome with finasteride. AJP 164, 1914–1915. https://doi.org/10.1176/appi.ajp.2007.07060978.

Bosse, G.D., Cadeddu, R., Floris, G., Farero, R.D., Vigato, E., Lee, S.J., Zhang, T., Gaikwad, N.W., Keefe, K.A., Phillips, P.E., Bortolato, M., Peterson, R.T., 2021. The 5α-reductase inhibitor finasteride reduces opioid self-administration in animal models of opioid use disorder. e143990 J. Clin. Invest. 131, 143990. https://doi.org/10.1172/JCI143990.

Bourque, M., Morissette, M., Di Paolo, T., 2024. Neuroactive steroids and Parkinson's disease: Review of human and animal studies. Neurosci. Biobehav. Rev. 156, 105479 https://doi.org/10.1016/j.neubiorev.2023.105479.

Bowlby, M.R., 1993. Pregnenolone sulfate potentiation of N-methyl-D-aspartate receptor channels in hippocampal neurons. Mol. Pharmacol. 43, 813–819.

Branca, C., Bortolato, M., 2024. The role of neuroactive steroids in tic disorders. Neurosci. Biobehav. Rev. 160, 105637 https://doi.org/10.1016/j.neubiorev.2024.105637.

Brodnik, Z.D., Batra, A., Oleson, E.B., España, R.A., 2019. Local GABAA receptor-mediated suppression of dopamine release within the nucleus accumbens. ACS Chem. Neurosci. 10, 1978–1985. https://doi.org/10.1021/acschemneuro.8b00268.

Brown, E.S., Park, J., Marx, C.E., Hynan, L.S., Gardner, C., Davila, D., Nakamura, A., Sunderajan, P., Lo, A., Holmes, T., 2014. A randomized, double-blind, placebo-controlled trial of pregnenolone for bipolar depression. Neuropsychopharmacology 39, 2867–2873. https://doi.org/10.1038/npp.2014.138.

Bullock, A., Kaul, I., Li, S., Silber, C., Doherty, J., Kanes, S.J., 2021. Zuranolone as an oral adjunct to treatment of Parkinsonian tremor: A phase 2, open-label study. J. Neurol. Sci. 421, 117277 https://doi.org/10.1016/j.jns.2020.117277.

Busquets-Garcia, A., Soria-Gómez, E., Redon, B., Mackenbach, Y., Vallée, M., Chaouloff, F., Varilh, M., Ferreira, G., Piazza, P.-V., Marsicano, G., 2017. Pregnenolone blocks cannabinoid-induced acute psychotic-like states in mice. Mol. Psychiatry 22, 1594–1603. https://doi.org/10.1038/mp.2017.4.

Cáceres, A.R.R., Cardone, D.A., Sanhueza, M. de L.Á., Bosch, I.M., Cuello-Carrión, F.D., Rodriguez, G.B., Scotti, L., Parborell, F., Halperin, J., Laconi, M.R., 2024. Local effect of allopregnanolone in rat ovarian steroidogenesis, follicular and corpora lutea development. Sci. Rep. 14, 6402. https://doi.org/10.1038/s41598-024-57102-1.

Cadeddu, R., Bäckström, T., Floris, G., Nordkild, P., Segerdahl, M., Bortolato, M., 2020. Isoallopregnanolone reduces tic-like behaviours in the D1CT-7 mouse model of Tourette syndrome. J. Neuroendocr. 32, e12754 https://doi.org/10.1111/jne.12754.

Cadeddu, R., Mosher, L.J., Nordkild, P., Gaikwad, N., Ratto, G.M., Scheggi, S., Bortolato, M., 2022. Acute stress impairs sensorimotor gating via the neurosteroid allopregnanolone in the prefrontal cortex. Neurobiol. Stress 21, 100489. https://doi.org/10.1016/j.ynstr.2022.100489.

Cadeddu, R., Van Zandt, M., Santovito, L.S., Odeh, K., Anderson, C.J., Flanagan, D., Nordkild, P., Pinna, G., Pittenger, C., Bortolato, M., 2023. Prefrontal allopregnanolone mediates the adverse effects of acute stress in a mouse model of tic pathophysiology. Neuropsychopharmacology 48, 1288–1299. https://doi.org/10.1038/s41386-023-01603-6.

Cai, H., Zhou, X., Dougherty, G.G., Reddy, R.D., Haas, G.L., Montrose, D.M., Keshavan, M., Yao, J.K., 2018. Pregnenolone-progesterone-allopregnanolone pathway as a potential therapeutic target in first-episode antipsychotic-naïve patients with schizophrenia. Psychoneuroendocrinology 90, 43–51. https://doi.org/10.1016/j.psyneuen.2018.02.004.

Cardinal, R.N., Pennicott, D.R., Sugathapala, C.L., Robbins, T.W., Everitt, B.J., 2001. Impulsive choice induced in rats by lesions of the nucleus accumbens core. Science 292, 2499–2501. https://doi.org/10.1126/science.1060818.

Castellanos, F.X., Tannock, R., 2002. Neuroscience of attention-deficit/hyperactivity disorder: the search for endophenotypes. Nat. Rev. Neurosci. 3, 617–628. https://doi.org/10.1038/nrn896.

Castelli, M.P., Casti, A., Casu, A., Frau, R., Bortolato, M., Spiga, S., Ennas, M.G., 2013. Regional distribution of 5α-reductase type 2 in the adult rat brain: an immunohistochemical analysis. Psychoneuroendocrinology 38, 281–293. https://doi.org/10.1016/j.psyneuen.2012.06.008.

Celotti, F., Melcangi, R.C., Martini, L., 1992. The 5 alpha-reductase in the brain: molecular aspects and relation to brain function. Front. Neuroendocr. 13, 163–215.

Ciccarelli, M., Griffiths, M.D., Cosenza, M., Nigro, G., D'Olimpio, F., 2020. Disordered gambling and attentional bias: The mediating role of risk-taking. J. Affect Disord. 272, 496–500. https://doi.org/10.1016/j.jad.2020.03.144.

Clark, L., Boileau, I., Zack, M., 2019. Neuroimaging of reward mechanisms in Gambling disorder: an integrative review. Mol. Psychiatry 24, 674–693. https://doi.org/10.1038/s41380-018-0230-2.

Clayton, A.H., Suthoff, E., Jain, R., Kosinski, M., Fridman, M., Deligiannidis, K.M., Meltzer-Brody, S., Chen, S.-Y., Gervitz, L., Huang, M.-Y., Trivedi, M., Bonthapally, V., 2024. The magnitude and sustainability of treatment benefit of zuranolone on function and well-being as assessed by the SF-36 in adult patients with MDD and PPD: An integrated analysis of 4 randomized clinical trials. J. Affect Disord. 351, 904–914. https://doi.org/10.1016/j.jad.2024.01.268.

Concas, A., Mostallino, M.C., Porcu, P., Follesa, P., Barbaccia, M.L., Trabucchi, M., Purdy, R.H., Grisenti, P., Biggio, G., 1998. Role of brain allopregnanolone in the plasticity of gamma-aminobutyric acid type A receptor in rat brain during pregnancy and after delivery. Proc. Natl. Acad. Sci. USA 95, 13284–13289. https://doi.org/10.1073/pnas.95.22.13284.

Corsi, S., Scheggi, S., Pardu, A., Braccagni, G., Caruso, D., Cioffi, L., Diviccaro, S., Gentile, M., Fanni, S., Stancampiano, R., Gambarana, C., Melcangi, R.C., Frau, R., Carta, M., 2023. Pregnenolone for the treatment of L-DOPA-induced dyskinesia in Parkinson's disease. Exp. Neurol. 363, 114370 https://doi.org/10.1016/j.expneurol.2023.114370.

Corsi, D.J., Walsh, L., Weiss, D., Hsu, H., El-Chaar, D., Hawken, S., Fell, D.B., Walker, M., 2019. Association between self-reported prenatal cannabis use and maternal, perinatal, and neonatal outcomes. JAMA 322, 145–152. https://doi.org/10.1001/jama.2019.8734.

Crowley, S.K., Girdler, S.S., 2014. Neurosteroid, GABAergic and hypothalamic pituitary adrenal (HPA) axis regulation: what is the current state of knowledge in humans? Psychopharmacol. (Berl.) 231, 3619–3634. https://doi.org/10.1007/s00213-014-3572-8.

Cushman, J.D., Moore, M.D., Jacobs, N.S., Olsen, R.W., Fanselow, M.S., 2011. Behavioral pharmacogenetic analysis on the role of the α4 GABA(A) receptor subunit in the ethanol-mediated impairment of hippocampus-dependent contextual learning. Alcohol Clin. Exp. Res. 35, 1948–1959. https://doi.org/10.1111/j.1530-0277.2011.01546.x.

Dazzi, L., Serra, M., Vacca, G., Ladu, S., Latrofa, A., Trapani, G., Biggio, G., 2002. Depletion of cortical allopregnanolone potentiates stress-induced increase in cortical dopamine output. Brain Res. 932, 135–139. https://doi.org/10.1016/s0006-8993(02)02290-4.

Debove, I., Paschen, S., Amstutz, D., Cardoso, F., Corvol, J.-C., Fung, V.S.C., Lang, A.E., Martinez Martin, P., Rodríguez-Oroz, M.C., Weintraub, D., Krack, P., Deuschl, G., the Members of the ICBD in PD Management Consensus Group, 2024. Management of impulse control and related disorders in Parkinson's Disease: An Expert Consensus. Mov. Disord. 39, 235–248. https://doi.org/10.1002/mds.29700.

Deligiannidis, K.M., Meltzer-Brody, S., Gunduz-Bruce, H., Doherty, J., Jonas, J., Li, S., Sankoh, A.J., Silber, C., Campbell, A.D., Werneburg, B., Kanes, S.J., Lasser, R., 2021. Effect of zuranolone vs placebo in postpartum depression: a randomized clinical trial. JAMA Psychiatry 78, 951–959. https://doi.org/10.1001/jamapsychiatry.2021.1559.

Deligiannidis, K.M., Meltzer-Brody, S., Maximos, B., Peeper, E.Q., Freeman, M., Lasser, R., Bullock, A., Kotecha, M., Li, S., Forrestal, F., Rana, N., Garcia, M., Leclair, B., Doherty, J., 2023. Zuranolone for the treatment of postpartum depression. Am. J. Psychiatry 180, 668–675. https://doi.org/10.1176/appi.ajp.20220785.

Deutch, A.Y., Roth, R.H., 1990. The determinants of stress-induced activation of the prefrontal cortical dopamine system. discussion 402-403 Prog. Brain Res. 85, 367–402. https://doi.org/10.1016/s0079-6123(08)62691-6.

Devoto, P., Frau, R., Bini, V., Pillolla, G., Saba, P., Flore, G., Corona, M., Marrosu, F., Bortolato, M., 2012. Inhibition of 5α-reductase in the nucleus accumbens counters sensorimotor gating deficits induced by dopaminergic activation. Psychoneuroendocrinology 37, 1630–1645. https://doi.org/10.1016/j.psyneuen.2011.09.018.

di Michele, F., Luchetti, S., Bernardi, G., Romeo, E., Longone, P., 2013. Neurosteroid and neurotransmitter alterations in Parkinson's disease. Front. Neuroendocr. 34, 132–142. https://doi.org/10.1016/j.yfrne.2013.03.001.

Di Paolo, T., 1994. Modulation of brain dopamine transmission by sex steroids. Rev Neurosci 5, 27–41. https://doi.org/10.1515/revneuro.1994.5.1.27.

Di Paolo, T., Lévesque, D., Daigle, M., 1986. A physiological dose of progesterone affects rat striatum biogenic amine metabolism. Eur. J. Pharmacol. 125, 11–16. https://doi.org/10.1016/0014-2999(86)90077-4.

Dluzen, D.E., Ramirez, V.D., 1984. Bimodal effect of progesterone on in vitro dopamine function of the rat corpus striatum. Neuroendocrinology 39, 149–155. https://doi.org/10.1159/000123971.

Dodd, M.L., Klos, K.J., Bower, J.H., Geda, Y.E., Josephs, K.A., Ahlskog, J.E., 2005. Pathological gambling caused by drugs used to treat Parkinson disease. Arch. Neurol. 62, 1377–1381. https://doi.org/10.1001/archneur.62.9.noc50009.

Dornellas, A.P.S., Macedo, G.C., McFarland, M.H., Gómez-A, A., O'Buckley, T.K., Da Cunha, C., Morrow, A.L., Robinson, D.L., 2020. Allopregnanolone decreases evoked dopamine release differently in rats by sex and estrous stage. Front. Pharmacol. 11, 608887 https://doi.org/10.3389/fphar.2020.608887.

Dubrovsky, B.O., 2005. Steroids, neuroactive steroids and neurosteroids in psychopathology. Prog. Neuropsychopharmacol. Biol. Psychiatry 29, 169–192. https://doi.org/10.1016/j.pnpbp.2004.11.001.

Epperson, C.N., Rubinow, D.R., Meltzer-Brody, S., Deligiannidis, K.M., Riesenberg, R., Krystal, A.D., Bankole, K., Huang, M.-Y., Li, H., Brown, C., Kanes, S.J., Lasser, R., 2023. Effect of brexanolone on depressive symptoms, anxiety, and insomnia in women with postpartum depression: Pooled analyses from 3 double-blind, randomized, placebo-controlled clinical trials in the HUMMINGBIRD clinical program. J. Affect Disord. 320, 353–359. https://doi.org/10.1016/j.jad.2022.09.143.

Eser, D., Baghai, T.C., Schüle, C., Nothdurfter, C., Rupprecht, R., 2008. Neuroactive steroids as endogenous modulators of anxiety. Curr. Pharm. Des. 14, 3525–3533. https://doi.org/10.2174/138161208786848838.

Estrada-Camarena, E., Contreras, C.M., Saavedra, M., Luna-Baltazar, I., López-Rubalcava, C., 2002. Participation of the lateral septal nuclei (LSN) in the antidepressant-like actions of progesterone in the forced swimming test (FST). Behavioural Brain Research 134, 175–183. https://doi.org/10.1016/S0166-4328(02)00023-2.

Fadalti, M., Petraglia, F., Luisi, S., Bernardi, F., Casarosa, E., Ferrari, E., Luisi, M., Saggese, G., Genazzani, A.R., Bernasconi, S., 1999. Changes of serum

allopregnanolone levels in the first 2 years of life and during pubertal development. Pedia Res. 46, 323–327. https://doi.org/10.1203/00006450-199909000-00013.
Fanni, S., Scheggi, S., Rossi, F., Tronci, E., Traccis, F., Stancampiano, R., De Montis, M.G., Devoto, P., Gambarana, C., Bortolato, M., Frau, R., Carta, M., 2019. 5alpha-reductase inhibitors dampen L-DOPA-induced dyskinesia via normalization of dopamine D1-receptor signaling pathway and D1-D3 receptor interaction. Neurobiol. Dis. 121, 120–130. https://doi.org/10.1016/j.nbd.2018.09.018.
Fernández-Ruiz, J.J., Amor, J.C., Ramos, J.A., 1989. Time-dependent effects of estradiol and progesterone on the number of striatal dopaminergic D2-receptors. Brain Res. 476, 388–395. https://doi.org/10.1016/0006-8993(89)91266-3.
Fine, J.D., Moreau, A.L., Karcher, N.R., Agrawal, A., Rogers, C.E., Barch, D.M., Bogdan, R., 2019. Association of prenatal cannabis exposure with psychosis proneness among children in the adolescent brain cognitive development (ABCD) study. JAMA Psychiatry 76, 762–764. https://doi.org/10.1001/jamapsychiatry.2019.0076.
Finn, D.A., Mark, G.P., Fretwell, A.M., Gililland-Kaufman, K.R., Strong, M.N., Ford, M. M., 2008. Reinstatement of ethanol and sucrose seeking by the neurosteroid allopregnanolone in C57BL/6 mice. Psychopharmacol. (Berl.) 201, 423–433. https://doi.org/10.1007/s00213-008-1303-8.
Finn, D.A., Sinnott, R.S., Ford, M.M., Long, S.L., Tanchuck, M.A., Phillips, T.J., 2004. Sex differences in the effect of ethanol injection and consumption on brain allopregnanolone levels in C57BL/6 mice. Neuroscience 123, 813–819. https://doi.org/10.1016/j.neuroscience.2003.11.017.
Fiorentini, C., Busi, C., Gorruso, E., Gotti, C., Spano, P., Missale, C., 2008. Reciprocal regulation of dopamine D1 and D3 receptor function and trafficking by heterodimerization. Mol. Pharmacol. 74, 59–69. https://doi.org/10.1124/mol.107.043885.
Fish, E.W., Whitman, B.J., DiBerto, J.F., Robinson, J.E., Morrow, A.L., Malanga, C.J., 2014. Effects of the neuroactive steroid allopregnanolone on intracranial self-stimulation in C57BL/6J mice. Psychopharmacol. (Berl.) 231, 3415–3423. https://doi.org/10.1007/s00213-014-3600-8.
Floris, G., Scheggi, S., Pes, R., Bortolato, M., 2022. The steroidogenic inhibitor finasteride reverses pramipexole-induced alterations in probability discounting. Brain Res. Bull. 181, 157–166. https://doi.org/10.1016/j.brainresbull.2022.01.020.
Fox, H.C., Sofuoglu, M., Morgan, P.T., Tuit, K.L., Sinha, R., 2013. The effects of exogenous progesterone on drug craving and stress arousal in cocaine dependence: impact of gender and cue type. Psychoneuroendocrinology 38, 1532–1544. https://doi.org/10.1016/j.psyneuen.2012.12.022.
Frau, R., Abbiati, F., Bini, V., Casti, A., Caruso, D., Devoto, P., Bortolato, M., 2015. Targeting neurosteroid synthesis as a therapy for schizophrenia-related alterations induced by early psychosocial stress. Schizophr Res 168, 640–648. https://doi.org/10.1016/j.schres.2015.04.044.
Frau, R., Bini, V., Pes, R., Pillolla, G., Saba, P., Devoto, P., Bortolato, M., 2014. Inhibition of 17α-hydroxylase/C17,20 lyase reduces gating deficits consequent to dopaminergic activation. Psychoneuroendocrinology 39, 204–213. https://doi.org/10.1016/j.psyneuen.2013.09.014.
Frau, R., Bortolato, M., 2019. Repurposing steroidogenesis inhibitors for the therapy of neuropsychiatric disorders: Promises and caveats. Neuropharmacology 147, 55–65. https://doi.org/10.1016/j.neuropharm.2018.05.013.
Frau, R., Melis, M., 2023. Sex-specific susceptibility to psychotic-like states provoked by prenatal THC exposure: Reversal by pregnenolone. J. Neuroendocr. 35, e13240 https://doi.org/10.1111/jne.13240.
Frau, R., Miczán, V., Traccis, F., Aroni, S., Pongor, C.I., Saba, P., Serra, V., Sagheddu, C., Fanni, S., Congiu, M., Devoto, P., Cheer, J.F., Katona, I., Melis, M., 2019. Prenatal THC exposure produces a hyperdopaminergic phenotype rescued by pregnenolone. Nat. Neurosci. 22, 1975–1985. https://doi.org/10.1038/s41593-019-0512-2.
Frau, R., Mosher, L.J., Bini, V., Pillolla, G., Pes, R., Saba, P., Fanni, S., Devoto, P., Bortolato, M., 2016. The neurosteroidogenic enzyme 5α-reductase modulates the role of D1 dopamine receptors in rat sensorimotor gating. Psychoneuroendocrinology 63, 59–67. https://doi.org/10.1016/j.psyneuen.2015.09.014.
Frau, R., Pillolla, G., Bini, V., Tambaro, S., Devoto, P., Bortolato, M., 2013. Inhibition of 5α-reductase attenuates behavioral effects of D1-, but not D2-like receptor agonists in C57BL/6 mice. Psychoneuroendocrinology 38, 542–551. https://doi.org/10.1016/j.psyneuen.2012.07.014.
Frau, R., Savoia, P., Fanni, S., Fiorentini, C., Fidalgo, C., Tronci, E., Stancampiano, R., Meloni, M., Cannas, A., Marrosu, F., Bortolato, M., Devoto, P., Missale, C., Carta, M., 2017. The 5-alpha reductase inhibitor finasteride reduces dyskinesia in a rat model of Parkinson's disease. Exp. Neurol. 291, 1–7. https://doi.org/10.1016/j.expneurol.2017.01.012.
Frau, R., Traccis, F., Concas, L., Cadeddu, R., Mosher, L.J., Nordkild, P., Gaikwad, N.W., Bortolato, M., 2023. Prefrontal allopregnanolone synergizes with D1 receptor activation to disrupt sensorimotor gating in male Sprague-Dawley rats. Psychopharmacol. (Berl.). https://doi.org/10.1007/s00213-023-06375-x.
Frye, C.A., Paris, J.J., Osborne, D.M., Campbell, J.C., Kippin, T.E., 2011. Prenatal stress alters progestogens to mediate susceptibility to sex-typical, stress-sensitive disorders, such as drug abuse: a review. Front. Psychiatry 2, 52. https://doi.org/10.3389/fpsyt.2011.00052.
Frye, C.A., Rhodes, M.E., Petralia, S.M., Walf, A.A., Sumida, K., Edinger, K.L., 2006. 3alpha-hydroxy-5alpha-pregnan-20-one in the midbrain ventral tegmental area mediates social, sexual, and affective behaviors. Neuroscience 138, 1007–1014. https://doi.org/10.1016/j.neuroscience.2005.06.015.
Frye, C.A., Sora, I., 2010. Progesterone reduces hyperactivity of female and male dopamine transporter knockout mice. Behav. Brain Res. 209, 59–65. https://doi.org/10.1016/j.bbr.2010.01.015.
Frye, C.A., Walf, A.A., 2010. Infusions of anti-sense oligonucleotides for DARPP-32 to the ventral tegmental area reduce effects of progesterone- and a dopamine type 1-like receptor agonist to facilitate lordosis. Behav. Brain Res. 206, 286–292. https://doi.org/10.1016/j.bbr.2009.09.028.
Fu, Y., Zhao, Y., Luan, W., Dong, L.-Y., Dong, Y., Lai, B., Zhu, Y., Zheng, P., 2010. Sigma-1 receptors amplify dopamine D1 receptor signaling at presynaptic sites in the prelimbic cortex. Biochim. Biophys. Acta 1803, 1396–1408. https://doi.org/10.1016/j.bbamcr.2010.08.005.
Garcia-Argibay, M., Hiyoshi, A., Fall, K., Montgomery, S., 2022. Association of 5α-Reductase Inhibitors With Dementia, Depression, and Suicide. JAMA Netw Open 5, e2248135. 10.1001/jamanetworkopen.2022.48135.
Geyer, M.A., 2006. The family of sensorimotor gating disorders: comorbidities or diagnostic overlaps? Neurotox. Res. 10, 211–220. https://doi.org/10.1007/BF03033358.
Geyer, M.A., Krebs-Thomson, K., Braff, D.L., Swerdlow, N.R., 2001. Pharmacological studies of prepulse inhibition models of sensorimotor gating deficits in schizophrenia: a decade in review. Psychopharmacol. (Berl.) 156, 117–154. https://doi.org/10.1007/s002130100811.
Giatti, S., Diviccaro, S., Cioffi, L., Cosimo Melcangi, R., 2024. Post-finasteride syndrome and post-ssri sexual dysfunction: two clinical conditions apparently distant, but very close. Front Neuroendocr. 72, 101114 https://doi.org/10.1016/j.yfrne.2023.101114.
Giatti, S., Garcia-Segura, L.M., Barreto, G.E., Melcangi, R.C., 2019. Neuroactive steroids, neurosteroidogenesis and sex. Prog. Neurobiol. 176, 1–17. https://doi.org/10.1016/j.pneurobio.2018.06.007.
Gibbs, T.T., Russek, S.J., Farb, D.H., 2006. Sulfated steroids as endogenous neuromodulators. Pharm. Biochem. Behav. 84, 555–567. https://doi.org/10.1016/j.pbb.2006.07.031.
Gilbert, D.L., Budman, C.L., Singer, H.S., Kurlan, R., Chipkin, R.E., 2014. A D1 receptor antagonist, ecopipam, for treatment of tics in Tourette syndrome. Clin Neuropharmacol 37, 26–30. 10.1097/WNF.0000000000000017.
Gilbert, D.L., Dure, L., Sethuraman, G., Raab, D., Lane, J., Sallee, F.R., 2003. Tic reduction with pergolide in a randomized controlled trial in children. Neurology 60, 606–611. https://doi.org/10.1212/01.wnl.0000044058.64647.7e.
Godar, S.C., Cadeddu, R., Floris, G., Mosher, L.J., Mi, Z., Jarmolowicz, D.P., Scheggi, S., Walf, A.A., Koonce, C.J., Frye, C.A., Muma, N.A., Bortolato, M., 2019. The steroidogenesis inhibitor finasteride reduces the response to both stressful and rewarding stimuli. Biomolecules 9, 749. https://doi.org/10.3390/biom9110749.
Gomez-Mancilla, B., Bédard, P.J., 1992. Effect of estrogen and progesterone on L-dopa induced dyskinesia in MPTP-treated monkeys. Neurosci. Lett. 135, 129–132. https://doi.org/10.1016/0304-3940(92)90152-w.
Griffin, L.D., Mellon, S.H., 1999. Selective serotonin reuptake inhibitors directly alter activity of neurosteroidogenic enzymes. Proc. Natl. Acad. Sci. USA 96, 13512–13517. https://doi.org/10.1073/pnas.96.23.13512.
Guillin, O., Diaz, J., Carroll, P., Griffon, N., Schwartz, J.C., Sokoloff, P., 2001. BDNF controls dopamine D3 receptor expression and triggers behavioural sensitization. Nature 411, 86–89. https://doi.org/10.1038/35075076.
Gunduz-Bruce, H., Silber, C., Kaul, I., Rothschild, A.J., Riesenberg, R., Sankoh, A.J., Li, H., Lasser, R., Zorumski, C.F., Rubinow, D.R., Paul, S.M., Jonas, J., Doherty, J.J., Kanes, S.J., 2019. Trial of SAGE-217 in patients with major depressive disorder. N. Engl. J. Med. 381, 903–911. https://doi.org/10.1056/NEJMoa1815981.
Hammes, J., Theis, H., Giehl, K., Hoenig, M.C., Greuel, A., Tittgemeyer, M., Timmermann, L., Fink, G.R., Drzezga, A., Eggers, C., van Eimeren, T., 2019. Dopamine metabolism of the nucleus accumbens and fronto-striatal connectivity modulate impulse control. Brain 142, 733–743. https://doi.org/10.1093/brain/awz007.
Haney, M., Vallée, M., Fabre, S., Collins Reed, S., Zanese, M., Campistron, G., Arout, C.A., Foltin, R.W., Cooper, Z.D., Kearney-Ramos, T., Metna, M., Justinova, Z., Schindler, C., Hebert-Chatelain, E., Bellocchio, L., Cathala, A., Bari, A., Serrat, R., Finlay, D.B., Caraci, F., Redon, B., Martín-García, E., Busquets-Garcia, A., Matias, I., Levin, F.R., Felpin, F.-X., Simon, N., Cota, D., Spampinato, U., Maldonado, R., Shaham, Y., Glass, M., Thomsen, L.L., Mengel, H., Marsicano, G., Monlezun, S., Revest, J.-M., Piazza, P.V., 2023. Signaling-specific inhibition of the CB1 receptor for cannabis use disorder: phase 1 and phase 2a randomized trials. Nat Med 29, 1487–1499. https://doi.org/10.1038/s41591-023-02381-w.
Harkany, T., Guzmán, M., Galve-Roperh, I., Berghuis, P., Devi, L.A., Mackie, K., 2007. The emerging functions of endocannabinoid signaling during CNS development. Trends Pharmacol. Sci. 28, 83–92. https://doi.org/10.1016/j.tips.2006.12.004.
Heydari, B., Le Mellédo, J.-M., 2002. Low pregnenolone sulphate plasma concentrations in patients with generalized social phobia. Psychol. Med. 32, 929–933. https://doi.org/10.1017/s0033291702005238.
Hidalgo-Lopez, E., Pletzer, B., 2017. Interactive effects of dopamine baseline levels and cycle phase on executive functions: the role of progesterone. Front. Neurosci. 11, 403. https://doi.org/10.3389/fnins.2017.00403.
Hoffman, D.C., Donovan, H., Cassella, J.V., 1993. The effects of haloperidol and clozapine on the disruption of sensorimotor gating induced by the noncompetitive glutamate antagonist MK-801. Psychopharmacol. (Berl.) 111, 339–344. https://doi.org/10.1007/BF02244950.
Horak, M., Vlcek, K., Chodounska, H., Vyklicky, L., 2006. Subtype-dependence of N-methyl-D-aspartate receptor modulation by pregnenolone sulfate. Neuroscience 137, 93–102. https://doi.org/10.1016/j.neuroscience.2005.08.058.
Howes, O.D., McCutcheon, R., Owen, M.J., Murray, R.M., 2017. The Role of Genes, Stress, and Dopamine in the Development of Schizophrenia. Biol. Psychiatry 81, 9–20. https://doi.org/10.1016/j.biopsych.2016.07.014.
Hrcka Krausova, B., Kysilov, B., Cerny, J., Vyklicky, V., Smejkalova, T., Ladislav, M., Balik, A., Korinek, M., Chodounska, H., Kudova, E., Vyklicky, L., 2020. Site of Action

Of Brain Neurosteroid Pregnenolone Sulfate at the N-methyl-D-Aspartate Receptor. J. Neurosci. 40, 5922–5936. https://doi.org/10.1523/JNEUROSCI.3010-19.2020.
Hurd, Y.L., Manzoni, O.J., Pletnikov, M.V., Lee, F.S., Bhattacharyya, S., Melis, M., 2019. Cannabis and the developing brain: insights into its long-lasting effects. J. Neurosci. 39, 8250–8258. https://doi.org/10.1523/JNEUROSCI.1165-19.2019.
Irwig, M.S., 2012. Depressive symptoms and suicidal thoughts among former users of finasteride with persistent sexual side effects. J. Clin. Psychiatry 73, 1220–1223. https://doi.org/10.4088/JCP.12m07887.
Irwin, R.P., Lin, S.Z., Rogawski, M.A., Purdy, R.H., Paul, S.M., 1994. Steroid potentiation and inhibition of N-methyl-D-aspartate receptor-mediated intracellular Ca++ responses: structure-activity studies. J. Pharmacol. Exp. Ther. 271, 677–682.
Jeon, N., Bortolato, M., 2020. What drugs modify the risk of iatrogenic impulse-control disorders in Parkinson's disease? A preliminary pharmacoepidemiologic study. PLoS One 15, e0227128. https://doi.org/10.1371/journal.pone.0227128.
Johansson, I.M., Birzniece, V., Lindblad, C., Olsson, T., Bäckström, T., 2002. Allopregnanolone inhibits learning in the Morris water maze. Brain Res. 934, 125–131. https://doi.org/10.1016/s0006-8993(02)02414-9.
Johansson, M., Strömberg, J., Ragagnin, G., Doverskog, M., Bäckström, T., 2016. GABAA receptor modulating steroid antagonists (GAMSA) are functional in vivo. J. Steroid Biochem. Mol. Biol., SI:Steroids Nerv. Syst. 160, 98–105. https://doi.org/10.1016/j.jsbmb.2015.10.019.
Kanes, S.J., Colquhoun, H., Doherty, J., Raines, S., Hoffmann, E., Rubinow, D.R., Meltzer-Brody, S., 2017. Open-label, proof-of-concept study of brexanolone in the treatment of severe postpartum depression. Hum. Psychopharmacol. 32, e2576 https://doi.org/10.1002/hup.2576.
Kanes, S., Colquhoun, H., Gunduz-Bruce, H., Raines, S., Arnold, R., Schacterle, A., Doherty, J., Epperson, C.N., Deligiannidis, K.M., Riesenberg, R., Hoffmann, E., Rubinow, D., Jonas, J., Paul, S., Meltzer-Brody, S., 2017. Brexanolone (SAGE-547 injection) in post-partum depression: a randomised controlled trial. Lancet 390, 480–489. https://doi.org/10.1016/S0140-6736(17)31264-3.
Kask, K., Bäckström, T., Nilsson, L.-G., Sundström-Poromaa, I., 2008. Allopregnanolone impairs episodic memory in healthy women. Psychopharmacol. (Berl.) 199, 161–168. https://doi.org/10.1007/s00213-008-1150-7.
Khisti, R.T., Deshpande, L.S., Chopde, C.T., 2002. The neurosteroid 3 alpha-hydroxy-5 alpha-pregnan-20-one affects dopamine-mediated behavior in rodents. Psychopharmacol. (Berl.) 161, 120–128. https://doi.org/10.1007/s00213-002-1006-5.
Kimball, A., Dichtel, L.E., Nyer, M.B., Mischoulon, D., Fisher, L.B., Cusin, C., Dording, C. M., Trinh, N.-H., Yeung, A., Haines, M.S., Sung, J.C., Pinna, G., Rasmusson, A.M., Carpenter, L.L., Fava, M., Klibanski, A., Miller, K.K., 2020. The allopregnanolone to progesterone ratio across the menstrual cycle and in menopause. Psychoneuroendocrinology 112, 104512. https://doi.org/10.1016/j.psyneuen.2019.104512.
Klein, M.O., Battagello, D.S., Cardoso, A.R., Hauser, D.N., Bittencourt, J.C., Correa, R.G., 2019. Dopamine: functions, signaling, and association with neurological diseases. Cell Mol. Neurobiol. 39, 31–59. https://doi.org/10.1007/s10571-018-0632-3.
Knight, S.R., Davidson, C., Young, A.M.J., Gibson, C.L., 2012. Allopregnanolone protects against dopamine-induced striatal damage after in vitro ischaemia via interaction at GABA A receptors. J. Neuroendocr. 24, 1135–1143. https://doi.org/10.1111/j.1365-2826.2012.02319.x.
Koethe, D., Bortolato, M., Piomelli, D., Leweke, F.M., 2008. Improvement of general symptoms in a chronic psychotic patient treated with finasteride: case report. Pharmacopsychiatry 41, 115–116. https://doi.org/10.1055/s-2008-1058110.
Korinek, M., Kapras, V., Vyklicky, V., Adamusova, E., Borovska, J., Vales, K., Stuchlik, A., Horak, M., Chodounska, H., Vyklicky, L., 2011. Neurosteroid modulation of N-methyl-D-aspartate receptors: molecular mechanism and behavioral effects. Steroids 76, 1409–1418. https://doi.org/10.1016/j.steroids.2011.09.002.
Kreinin, A., Bawakny, N., Ritsner, M.S., 2017. Adjunctive Pregnenolone Ameliorates the Cognitive Deficits in Recent-Onset Schizophrenia: An 8-Week, Randomized, Double-Blind, Placebo-Controlled Trial. Clin Schizophr Relat Psychoses 10, 201–210. https://doi.org/10.3371/CSRP.KRBA.013114.
Laconi, M.R., Cabrera, R.J., 2002. Effect of centrally injected allopregnanolone on sexual receptivity, luteinizing hormone release, hypothalamic dopamine turnover, and release in female rats. Endocrine 17, 77–83. https://doi.org/10.1385/ENDO:17:2:077.
Lambert, J.J., Cooper, M.A., Simmons, R.D.J., Weir, C.J., Belelli, D., 2009. Neurosteroids: endogenous allosteric modulators of GABA(A) receptors. Psychoneuroendocrinology 34 (Suppl 1), S48–58. https://doi.org/10.1016/j.psyneuen.2009.08.009.
Laurine, E., Lafitte, D., Grégoire, C., Sérée, E., Loret, E., Douillard, S., Michel, B., Briand, C., Verdier, J.-M., 2003. Specific binding of dehydroepiandrosterone to the N terminus of the microtubule-associated protein MAP2. J. Biol. Chem. 278, 29979–29986. https://doi.org/10.1074/jbc.M303242200.
Lévesque, D., Di Paolo, T., 1993. Modulation by estradiol and progesterone of the GTP effect on striatal D-2 dopamine receptors. Biochem Pharmacol. 45, 723–733. https://doi.org/10.1016/0006-2952(93)90148-p.
Luchetti, S., Huitinga, I., Swaab, D.F., 2011. Neurosteroid and GABA-A receptor alterations in Alzheimer's disease, Parkinson's disease and multiple sclerosis. Neuroscience 191, 6–21. https://doi.org/10.1016/j.neuroscience.2011.04.010.
Luchetti, S., Liere, P., Pianos, A., Verwer, R.W.H., Sluiter, A., Huitinga, I., Schumacher, M., Swaab, D.F., Mason, M.R.J., 2023. Disease stage-dependent changes in brain levels and neuroprotective effects of neuroactive steroids in Parkinson's disease. Neurobiol. Dis. 183, 106169 https://doi.org/10.1016/j.nbd.2023.106169.
Luisi, S., Petraglia, F., Benedetto, C., Nappi, R.E., Bernardi, F., Fadalti, M., Reis, F.M., Luisi, M., Genazzani, A.R., 2000. Serum allopregnanolone levels in pregnant women: changes during pregnancy, at delivery, and in hypertensive patients. J. Clin. Endocrinol. Metab. 85, 2429–2433. https://doi.org/10.1210/jcem.85.7.6675.
Luján, M.Á., Young-Morrison, R., Aroni, S., Katona, I., Melis, M., Cheer, J., 2024. Dynamic Overrepresentation of Accumbal Cues in Food- and Opioid-Seeking Rats after Prenatal THC Exposure. bioRxiv 2024.05.06.592839. https://doi.org/10.1101/2024.05.06.592839.
Lundgren, P., Strömberg, J., Bäckström, T., Wang, M., 2003. Allopregnanolone-stimulated GABA-mediated chloride ion flux is inhibited by 3beta-hydroxy-5alpha-pregnan-20-one (isoallopregnanolone). Brain Res. 982, 45–53. https://doi.org/10.1016/s0006-8993(03)02939-1.
Luscher, B., Shen, Q., Sahir, N., 2011. The GABAergic deficit hypothesis of major depressive disorder. Mol. Psychiatry 16, 383–406. https://doi.org/10.1038/mp.2010.120.
MacKenzie, E.M., Odontiadis, J., Le Mellédo, J.-M., Prior, T.I., Baker, G.B.I., 2007. The relevance of neuroactive steroids in schizophrenia, depression, and anxiety disorders. Cell Mol. Neurobiol. 27, 541–574. https://doi.org/10.1007/s10571-006-9086-0.
Madden, G.J., Johnson, P.S., Brewer, A.T., Pinkston, J.W., Fowler, S.C., 2010. Effects of pramipexole on impulsive choice in male wistar rats. Exp. Clin. Psychopharmacol. 18, 267–276. https://doi.org/10.1037/a0019244.
Malayev, A., Gibbs, T.T., Farb, D.H., 2002. Inhibition of the NMDA response by pregnenolone sulphate reveals subtype selective modulation of NMDA receptors by sulphated steroids. Br. J. Pharm. 135, 901–909. https://doi.org/10.1038/sj.bjp.0704543.
Mandy, M., Nyirenda, M., 2018. Developmental Origins of Health and Disease: the relevance to developing nations. Int. Health 10, 66–70. https://doi.org/10.1093/inthealth/ihy006.
Mani, S.K., Fienberg, A.A., O'Callaghan, J.P., Snyder, G.L., Allen, P.B., Dash, P.K., Moore, A.N., Mitchell, A.J., Bibb, J., Greengard, P., O'Malley, B.W., 2000. Requirement for DARPP-32 in progesterone-facilitated sexual receptivity in female rats and mice. Science 287, 1053–1056. https://doi.org/10.1126/science.287.5455.1053.
Mansbach, R.S., Geyer, M.A., 1989. Effects of phencyclidine and phencyclidine biologs on sensorimotor gating in the rat. Neuropsychopharmacology 2, 299–308. https://doi.org/10.1016/0893-133x(89)90035-3.
Marcellino, D., Ferré, S., Casadó, V., Cortés, A., Le Foll, B., Mazzola, C., Drago, F., Saur, O., Stark, H., Soriano, A., Barnes, C., Goldberg, S.R., Lluis, C., Fuxe, K., Franco, R., 2008. Identification of dopamine D1-D3 receptor heteromers. Indications for a role of synergistic D1-D3 receptor interactions in the striatum. J. Biol. Chem. 283, 26016–26025. https://doi.org/10.1074/jbc.M710349200.
Marx, C.E., Bradford, D.W., Hamer, R.M., Naylor, J.C., Allen, T.B., Lieberman, J.A., Strauss, J.L., Kilts, J.D., 2011. Pregnenolone as a novel therapeutic candidate in schizophrenia: emerging preclinical and clinical evidence. Neuroscience 191, 78–90. https://doi.org/10.1016/j.neuroscience.2011.06.076.
Marx, C.E., Keefe, R.S.E., Buchanan, R.W., Hamer, R.M., Kilts, J.D., Bradford, D.W., Strauss, J.L., Naylor, J.C., Payne, V.M., Lieberman, J.A., Savitz, A.J., Leimone, L.A., Dunn, L., Porcu, P., Morrow, A.L., Shampine, L.J., 2009. Proof-of-concept trial with the neurosteroid pregnenolone targeting cognitive and negative symptoms in schizophrenia. Neuropsychopharmacology 34, 1885–1903. https://doi.org/10.1038/npp.2009.26.
Marx, C.E., Lee, J., Subramaniam, M., Rapisarda, A., Bautista, D.C.T., Chan, E., Kilts, J. D., Buchanan, R.W., Wai, E.P., Verma, S., Sim, K., Hariram, J., Jacob, R., Keefe, R.S. E., Chong, S.A., 2014. Proof-of-concept randomized controlled trial of pregnenolone in schizophrenia. Psychopharmacol. (Berl.) 231, 3647–3662. https://doi.org/10.1007/s00213-014-3673-4.
Marx, C.E., Stevens, R.D., Shampine, L.J., Uzunova, V., Trost, W.T., Butterfield, M.I., Massing, M.W., Hamer, R.M., Morrow, A.L., Lieberman, J.A., 2006. Neuroactive steroids are altered in schizophrenia and bipolar disorder: relevance to pathophysiology and therapeutics. Neuropsychopharmacology 31, 1249–1263. https://doi.org/10.1038/sj.npp.1300952.
McInnes, K.J., Kenyon, C.J., Chapman, K.E., Livingstone, D.E.W., Macdonald, L.J., Walker, B.R., Andrew, R., 2004. 5alpha-reduced glucocorticoids, novel endogenous activators of the glucocorticoid receptor. J. Biol. Chem. 279, 22908–22912. https://doi.org/10.1074/jbc.M402822200.
Melcangi, R.C., Caruso, D., Levandis, G., Abbiati, F., Armentero, M.-T., Blandini, F., 2012. Modifications of neuroactive steroid levels in an experimental model of nigrostriatal degeneration: potential relevance to the pathophysiology of Parkinson's disease. J. Mol. Neurosci. 46, 177–183. https://doi.org/10.1007/s12031-011-9570-y.
Melcangi, R.C., Panzica, G.C., 2006. Neuroactive steroids: old players in a new game. Neuroscience 138, 733–739. https://doi.org/10.1016/j.neuroscience.2005.10.066.
Mellon, S.H., Vaudry, H., 2001. Biosynthesis of neurosteroids and regulation of their synthesis. Int Rev. Neurobiol. 46 33–78. https://doi.org/10.1016/s0074-7742(01)46058-2.
Mienville, J.M., Vicini, S., 1989. Pregnenolone sulfate antagonizes GABAA receptor-mediated currents via a reduction of channel opening frequency. Brain Res. 489, 190–194. https://doi.org/10.1016/0006-8993(89)90024-3.
Milivojevic, V., Charron, L., Fogelman, N., Hermes, G., Sinha, R., 2022. Pregnenolone Reduces Stress-Induced Craving, Anxiety, and Autonomic Arousal in Individuals with Cocaine Use Disorder. Biomolecules 12, 1593. https://doi.org/10.3390/biom12111593.
Miller, W.L., Bose, H.S., 2011. Early steps in steroidogenesis: intracellular cholesterol trafficking. J. Lipid Res 52, 2111–2135. https://doi.org/10.1194/jlr.R016675.
Monnet, F.P., Maurice, T., 2006. The sigma1 protein as a target for the non-genomic effects of neuro(active)steroids: molecular, physiological, and behavioral aspects. J. Pharm. Sci. 100, 93–118. https://doi.org/10.1254/jphs.cr0050032.

Montagnese, S., Lauridsen, M., Vilstrup, H., Zarantonello, L., Lakner, G., Fitilev, S., Zupanets, I., Kozlova, I., Bunkova, E., Tomasiewicz, K., Berglund, J.E., Rorsman, F., Hagström, H., Kechagias, S., Ocklind, C.E., Mauney, J., Thunarf, F., Mokhatarani, M., Bäckström, T., Doverskog, M., Lins, L.-E., Månsson, M., Samuelson, P., Nilsson, D., Schalling, M., Johansson, M., Arlander, E., Scharschmidt, B.F., 2021. A pilot study of golexanolone, a new GABA-A receptor-modulating steroid antagonist, in patients with covert hepatic encephalopathy. J. Hepatol. 75, 98–107. https://doi.org/10.1016/j.jhep.2021.03.012.

Morris, C.V., DiNieri, J.A., Szutorisz, H., Hurd, Y.L., 2011. Molecular mechanisms of maternal cannabis and cigarette use on human neurodevelopment. Eur. J. Neurosci. 34, 1574–1583. https://doi.org/10.1111/j.1460-9568.2011.07884.x.

Mosher, L.J., Godar, S.C., Nelson, M., Fowler, S.C., Pinna, G., Bortolato, M., 2017. Allopregnanolone mediates the exacerbation of Tourette-like responses by acute stress in mouse models. Sci. Rep. 7, 3348. https://doi.org/10.1038/s41598-017-03649-1.

Motzo, C., Porceddu, M.L., Maira, G., Flore, G., Concas, A., Dazzi, L., Biggio, G., 1996. Inhibition of basal and stress-induced dopamine release in the cerebral cortex and nucleus accumbens of freely moving rats by the neurosteroid allopregnanolone. J. Psychopharmacol. 10, 266–272. https://doi.org/10.1177/026988119601000402.

Murakami, K., Fellous, A., Baulieu, E.E., Robel, P., 2000. Pregnenolone binds to microtubule-associated protein 2 and stimulates microtubule assembly. Proc. Natl. Acad. Sci. USA 97, 3579–3584. https://doi.org/10.1073/pnas.97.7.3579.

Muroni, A., Paba, S., Puligheddu, M., Marrosu, F., Bortolato, M., 2011. A preliminary study of finasteride in Tourette syndrome. Mov. Disord. 26, 2146–2147. https://doi.org/10.1002/mds.23810.

Murray, A.M., Ryoo, H.L., Gurevich, E., Joyce, J.N., 1994. Localization of dopamine D3 receptors to mesolimbic and D2 receptors to mesostriatal regions of human forebrain. Proc. Natl. Acad. Sci. USA 91, 11271–11275. https://doi.org/10.1073/pnas.91.23.11271.

Nashwan, A.J., Rehan, S.T., Imran, L., Abbas, S.G., Khan, S.F., 2024. Exploring the clinical potentials of zuranolone in managing postpartum depression: A new therapeutic horizon. Prog. Neuropsychopharmacol. Biol. Psychiatry 132, 110983. https://doi.org/10.1016/j.pnpbp.2024.110983.

Navarro, G., Moreno, E., Aymerich, M., Marcellino, D., McCormick, P.J., Mallol, J., Cortés, A., Casadó, V., Canela, E.I., Ortiz, J., Fuxe, K., Lluís, C., Ferré, S., Franco, R., 2010. Direct involvement of sigma-1 receptors in the dopamine D1 receptor-mediated effects of cocaine. Proc. Natl. Acad. Sci. USA 107, 18676–18681. https://doi.org/10.1073/pnas.1008911107.

Nezhadi, A., Sheibani, V., Esmaeilpour, K., Shabani, M., Esmaeili-Mahani, S., 2016. Neurosteroid allopregnanolone attenuates cognitive dysfunctions in 6-OHDA-induced rat model of Parkinson's disease. Behav. Brain Res. 305, 258–264. https://doi.org/10.1016/j.bbr.2016.03.019.

Nickel, J.C., 2004. Comparison of clinical trials with finasteride and dutasteride. Rev. Urol. 6 (Suppl 9). , S31-39.

Nickel, J.C., Barkin, J., Koch, C., Dupont, C., Elhilali, M., 2008. Finasteride monotherapy maintains stable lower urinary tract symptoms in men with benign prostatic hyperplasia following cessation of alpha blockers. Can. Urol. Assoc. J. 2, 16–21. https://doi.org/10.5489/cuaj.520.

Nicoletti, A., Arabia, G., Pugliese, P., Nicoletti, G., Torchia, G., Condino, F., Morgante, L., Quattrone, A., Zappia, M., 2007. Hormonal replacement therapy in women with Parkinson disease and levodopa-induced dyskinesia: a crossover trial. Clin. Neuropharmacol. 30, 276–280. https://doi.org/10.1097/wnf.0b013e318050c9f9.

Normington, K., Russell, D.W., 1992. Tissue distribution and kinetic characteristics of rat steroid 5 alpha-reductase isozymes. Evidence for distinct physiological functions. J. Biol. Chem. 267, 19548–19554.

Orrù, M., Strathman, H.J., Floris, G., Scheggi, S., Levant, B., Bortolato, M., 2020. The adverse effects of pramipexole on probability discounting are not reversed by acute D2 or D3 receptor antagonism. Eur. Neuropsychopharmacol. 32, 104–119. https://doi.org/10.1016/j.euroneuro.2020.01.005.

Osuji, I.J., Vera-Bolaños, E., Carmody, T.J., Brown, E.S., 2010. Pregnenolone for cognition and mood in dual diagnosis patients. Psychiatry Res. 178, 309–312. https://doi.org/10.1016/j.psychres.2009.09.006.

Paden, C.M., McEwen, B.S., Fishman, J., Snyder, L., DeGroff, V., 1982. Competition by estrogens for catecholamine receptor binding in vitro. J. Neurochem. 39, 512–520. https://doi.org/10.1111/j.1471-4159.1982.tb03974.x.

Papadopoulos, V., Miller, W.L., 2012. Role of mitochondria in steroidogenesis. Best. Pract. Res. Clin. Endocrinol. Metab. 26, 771–790. https://doi.org/10.1016/j.beem.2012.05.002.

Park-Chung, M., Wu, F.S., Farb, D.H., 1994. 3 alpha-Hydroxy-5 beta-pregnan-20-one sulfate: a negative modulator of the NMDA-induced current in cultured neurons. Mol. Pharmacol. 46, 146–150.

Park-Chung, M., Wu, F.S., Purdy, R.H., Malayev, A.A., Gibbs, T.T., Farb, D.H., 1997. Distinct sites for inverse modulation of N-methyl-D-aspartate receptors by sulfated steroids. Mol. Pharmacol. 52, 1113–1123. https://doi.org/10.1124/mol.52.6.1113.

Paul, S.E., Hatoum, A.S., Fine, J.D., Johnson, E.C., Hansen, I., Karcher, N.R., Moreau, A. L., Bondy, E., Qu, Y., Carter, E.B., Rogers, C.E., Agrawal, A., Barch, D.M., Bogdan, R., 2021. Associations between prenatal cannabis exposure and childhood outcomes: results from the ABCD study. JAMA Psychiatry 78, 64–76. https://doi.org/10.1001/jamapsychiatry.2020.2902.

Paul, S.M., Purdy, R.H., 1992. Neuroactive steroids. FASEB J. 6, 2311–2322.

Pavón, N., Martín, A.B., Mendialdua, A., Moratalla, R., 2006. ERK phosphorylation and FosB expression are associated with L-DOPA-induced dyskinesia in hemiparkinsonian mice. Biol Psychiatry 59, 64–74. https://doi.org/10.1016/j.biopsych.2005.05.044.

Perry, W., Minassian, A., Feifel, D., Braff, D.L., 2001. Sensorimotor gating deficits in bipolar disorder patients with acute psychotic mania. Biol. Psychiatry 50, 418–424. https://doi.org/10.1016/s0006-3223(01)01184-2.

Pes, R., Godar, S.C., Fox, A.T., Burgeno, L.M., Strathman, H.J., Jarmolowicz, D.P., Devoto, P., Levant, B., Phillips, P.E., Fowler, S.C., Bortolato, M., 2017. Pramipexole enhances disadvantageous decision-making: Lack of relation to changes in phasic dopamine release. Neuropharmacology 114, 77–87. https://doi.org/10.1016/j.neuropharm.2016.11.014.

Peters, J., Vega, T., Weinstein, D., Mitchell, J., Kayser, A., 2020. Dopamine and Risky Decision-Making in Gambling Disorder. ENEURO.0461-19.2020 eNeuro 7. https://doi.org/10.1523/ENEURO.0461-19.2020.

Petralia, S.M., Frye, C.A., 2006. In the ventral tegmental area, G-proteins mediate progesterone's actions at dopamine type 1 receptors for lordosis of rats and hamsters. Psychopharmacol. (Berl.) 186, 133–142. https://doi.org/10.1007/s00213-006-0311-9.

Pineles, S.L., Nillni, Y.I., Pinna, G., Irvine, J., Webb, A., Arditte Hall, K.A., Hauger, R., Miller, M.W., Resick, P.A., Orr, S.P., Rasmusson, A.M., 2018. PTSD in women is associated with a block in conversion of progesterone to the GABAergic neurosteroids allopregnanolone and pregnanolone measured in plasma. Psychoneuroendocrinology 93, 133–141. https://doi.org/10.1016/j.psyneuen.2018.04.024.

Pinna, G., Almeida, F.B., Davis, J.M., 2022. Allopregnanolone in Postpartum Depression. Front. Glob. Women's. Health 3, 823616. https://doi.org/10.3389/fgwh.2022.823616.

Pinna, G., Dong, E., Matsumoto, K., Costa, E., Guidotti, A., 2003. In socially isolated mice, the reversal of brain allopregnanolone down-regulation mediates the anti-aggressive action of fluoxetine. Proc. Natl. Acad. Sci. USA 100, 2035–2040. https://doi.org/10.1073/pnas.0337642100.

Pinna, G., Rasmusson, A.M., 2014. Ganaxolone improves behavioral deficits in a mouse model of post-traumatic stress disorder. Front Cell Neurosci 8, 256. https://doi.org/10.3389/fncel.2014.00256.

Pisu, M.G., Concas, L., Siddi, C., Serra, M., Porcu, P., 2022. The allopregnanolone response to acute stress in females: preclinical and clinical studies. Biomolecules 12, 1262. https://doi.org/10.3390/biom12091262.

Porcu, P., Barron, A.M., Frye, C.A., Walf, A.A., Yang, S.-Y., He, X.-Y., Morrow, A.L., Panzica, G.C., Melcangi, R.C., 2016. Neurosteroidogenesis today: novel targets for neuroactive steroid synthesis and action and their relevance for translational research. J. Neuroendocr. 28, 12351. https://doi.org/10.1111/jne.12351.

Purves-Tyson, T.D., Owens, S.J., Double, K.L., Desai, R., Handelsman, D.J., Weickert, C. S., 2014. Testosterone induces molecular changes in dopamine signaling pathway molecules in the adolescent male rat nigrostriatal pathway. PLoS One 9, e91151. https://doi.org/10.1371/journal.pone.0091151.

Rabinowitz, A., Cohen, S.J., Finn, D.A., Stackman, R.W., 2014. The neurosteroid allopregnanolone impairs object memory and contextual fear memory in male C57BL/6J mice. Horm. Behav. 66, 238–246. https://doi.org/10.1016/j.yhbeh.2014.05.005.

Rasmusson, A.M., Pinna, G., Paliwal, P., Weisman, D., Gottschalk, C., Charney, D., Krystal, J., Guidotti, A., 2006. Decreased cerebrospinal fluid allopregnanolone levels in women with posttraumatic stress disorder. Biol. Psychiatry 60, 704–713. https://doi.org/10.1016/j.biopsych.2006.03.026.

Riggio, O., Ridola, L., Pasquale, C., Nardelli, S., Pentassuglio, I., Moscucci, F., Merli, M., 2011. Evidence of persistent cognitive impairment after resolution of overt hepatic encephalopathy. Clin. Gastroenterol. Hepatol. 9, 181–183. https://doi.org/10.1016/j.cgh.2010.10.002.

Ringuet, H., Pelletier, G., Brazeau, P., Gaudreau, P., Guilbault, L.A., Morisset, J., Couture, Y., Petitclerc, D., 1994. Long-term effects of human growth hormone-releasing hormone and photoperiod on hormone release and puberty in dairy heifers. J. Anim. Sci. 72, 2709–2717. https://doi.org/10.2527/1994.72102709x.

Ritsner, M.S., 2010. Pregnenolone, dehydroepiandrosterone, and schizophrenia: alterations and clinical trials. CNS Neurosci. Ther. 16, 32–44. https://doi.org/10.1111/j.1755-5949.2009.00118.x.

Ritsner, M.S., Bawakny, H., Kreinin, A., 2014. Pregnenolone treatment reduces severity of negative symptoms in recent-onset schizophrenia: an 8-week, double-blind, randomized add-on two-center trial. Psychiatry Clin Neurosci 68, 432–440. https://doi.org/10.1111/pcn.12150.

Robel, P., Baulieu, E.E., 1995. Neurosteroids: biosynthesis and function. Crit. Rev. Neurobiol. 9, 383–394.

Rodrìguez-Landa, J.F., Contreras, C.M., Bernal-Morales, B., Gutièrrez-Garcìa, A.G., Saavedra, M., 2007. Allopregnanolone reduces immobility in the forced swimming test and increases the firing rate of lateral septal neurons through actions on the GABAA receptor in the rat. J Psychopharmacol 21, 76–84. https://doi.org/10.1177/0269881106064203.

Romieu, P., Lucas, M., Maurice, T., 2006. Sigma1 receptor ligands and related neuroactive steroids interfere with the cocaine-induced state of memory. Neuropsychopharmacology 31, 1431–1443. https://doi.org/10.1038/sj.npp.1300885.

Romieu, P., Martin-Fardon, R., Bowen, W.D., Maurice, T., 2003. Sigma 1 receptor-related neuroactive steroids modulate cocaine-induced reward. J. Neurosci. 23, 3572–3576. https://doi.org/10.1523/JNEUROSCI.23-09-03572.2003.

Rougé-Pont, F., Mayo, W., Marinelli, M., Gingras, M., Le Moal, M., Piazza, P.V., 2002. The neurosteroid allopregnanolone increases dopamine release and dopaminergic response to morphine in the rat nucleus accumbens. Eur. J. Neurosci. 16, 169–173. https://doi.org/10.1046/j.1460-9568.2002.02084.x.

Rylander, D., Parent, M., O'Sullivan, S.S., Dovero, S., Lees, A.J., Bezard, E., Descarries, L., Cenci, M.A., 2010. Maladaptive plasticity of serotonin axon terminals in levodopa-induced dyskinesia. Ann. Neurol. 68, 619–628. https://doi.org/10.1002/ana.22097.

Sagheddu, C., Traccis, F., Serra, V., Congiu, M., Frau, R., Cheer, J.F., Melis, M., 2021. Mesolimbic dopamine dysregulation as a signature of information processing deficits imposed by prenatal THC exposure. Prog. Neuropsychopharmacol. Biol. Psychiatry 105, 110128. https://doi.org/10.1016/j.pnpbp.2020.110128.

Saigusa, T., Takada, K., Baker, S.C., Kumar, R., Stephenson, J.D., 1997. Dopamine efflux in the rat nucleus accumbens evoked by dopamine receptor stimulation in the entorhinal cortex is modulated by oestradiol and progesterone. Synapse 25, 37–43. https://doi.org/10.1002/(SICI)1098-2396(199701)25:1<37::AID-SYN5>3.0.CO;2-G.

Salamone, J.D., Correa, M., 2012. The mysterious motivational functions of mesolimbic dopamine. Neuron 76, 470–485. https://doi.org/10.1016/j.neuron.2012.10.021.

Sánchez, M.G., Bourque, M., Morissette, M., Di Paolo, T., 2010. Steroids-dopamine interactions in the pathophysiology and treatment of CNS disorders. CNS Neurosci Ther 16, e43–71. https://doi.org/10.1111/j.1755-5949.2010.00163.x.

Sandor, P., 2003. Pharmacological management of tics in patients with TS. J. Psychosom. Res. 55, 41–48. https://doi.org/10.1016/s0022-3999(03)00060-6.

Santini, E., Valjent, E., Usiello, A., Carta, M., Borgkvist, A., Girault, J.-A., Hervé, D., Greengard, P., Fisone, G., 2007. Critical involvement of cAMP/DARPP-32 and extracellular signal-regulated protein kinase signaling in L-DOPA-induced dyskinesia. J Neurosci 27, 6995–7005. https://doi.org/10.1523/JNEUROSCI.0852-07.2007.

Scheggi, S., De Montis, M.G., Gambarana, C., 2018. DARPP-32 in the orchestration of responses to positive natural stimuli. J. Neurochem. 147, 439–453. https://doi.org/10.1111/jnc.14558.

Scheggi, S., Rossi, F., Corsi, S., Fanni, S., Tronci, E., Ludovica, C., Vargiu, R., Gambarana, C., Muñoz, A., Stancampiano, R., Björklund, A., Carta, M., 2020. BDNF Overexpression Increases Striatal D3 Receptor Level at Striatal Neurons and Exacerbates D1-Receptor Agonist-Induced Dyskinesia. J. Park. Dis. 10, 1503–1514. https://doi.org/10.3233/JPD-202061.

Schwabe, K., McIntyre, D.C., Poulter, M.O., 2007. The neurosteroid THDOC differentially affects spatial behavior and anesthesia in Slow and Fast kindling rat strains. Behav. Brain Res. 178, 283–292. https://doi.org/10.1016/j.bbr.2007.01.005.

Sedlácek, M., Korínek, M., Petrovic, M., Cais, O., Adamusová, E., Chodounská, H., Vyklický, L., 2008. Neurosteroid modulation of ionotropic glutamate receptors and excitatory synaptic transmission. Physiol. Res. 57 Suppl. 3 S49–S57. https://doi.org/10.33549/physiolres.931600.

Serra, M., Pisu, M.G., Littera, M., Papi, G., Sanna, E., Tuveri, F., Usala, L., Purdy, R.H., Biggio, G., 2000. Social isolation-induced decreases in both the abundance of neuroactive steroids and GABA(A) receptor function in rat brain. J. Neurochem. 75, 732–740. https://doi.org/10.1046/j.1471-4159.2000.0750732.x.

Smolders, I., De Klippel, N., Sarre, S., Ebinger, G., Michotte, Y., 1995. Tonic GABA-ergic modulation of striatal dopamine release studied by in vivo microdialysis in the freely moving rat. Eur. J. Pharmacol. 284, 83–91. https://doi.org/10.1016/0014-2999(95)00369-v.

Sokoloff, P., Leriche, L., Diaz, J., Louvel, J., Pumain, R., 2013. Direct and indirect interactions of the dopamine D_3 receptor with glutamate pathways: implications for the treatment of schizophrenia. Naunyn Schmiedebergs Arch Pharmacol 386, 107–124. https://doi.org/10.1007/s00210-012-0797-0.

Solís, O., Garcia-Montes, J.R., González-Granillo, A., Xu, M., Moratalla, R., 2017. Dopamine D3 Receptor Modulates l-DOPA-Induced Dyskinesia by Targeting D1 Receptor-Mediated Striatal Signaling. Cereb. Cortex 27, 435–446. https://doi.org/10.1093/cercor/bhv231.

Spivak, C.E., 1994. Desensitization and noncompetitive blockade of GABAA receptors in ventral midbrain neurons by a neurosteroid dehydroepiandrosterone sulfate. Synapse 16, 113–122. https://doi.org/10.1002/syn.890160205.

Sripada, R.K., Marx, C.E., King, A.P., Rampton, J.C., Ho, S.S., Liberzon, I., 2013. Allopregnanolone elevations following pregnenolone administration are associated with enhanced activation of emotion regulation neurocircuits. Biol. Psychiatry 73, 1045–1053. https://doi.org/10.1016/j.biopsych.2012.12.008.

Steeves, T.D.L., Miyasaki, J., Zurowski, M., Lang, A.E., Pellecchia, G., Van Eimeren, T., Rusjan, P., Houle, S., Strafella, A.P., 2009. Increased striatal dopamine release in Parkinsonian patients with pathological gambling: a [11C] raclopride PET study. Brain 132, 1376–1385. https://doi.org/10.1093/brain/awp054.

Stocco, D.M., 2000. The role of the StAR protein in steroidogenesis: challenges for the future. J. Endocrinol. 164, 247–253. https://doi.org/10.1677/joe.0.1640247.

Stomati, M., Genazzani, A.D., Petraglia, F., Genazzani, A.R., 1998. Contraception as prevention and therapy: sex steroids and the brain. Eur. J. Contracept. Reprod. Health Care 3, 21–28. https://doi.org/10.3109/13625189809167481.

Suthoff, E., Kosinski, M., Arnaud, A., Hodgkins, P., Gunduz-Bruce, H., Lasser, R., Silber, C., Sankoh, A.J., Li, H., Werneburg, B., Jonas, J., Doherty, J., Kanes, S.J., Bonthapally, V., 2022. Patient-reported health-related quality of life from a randomized, placebo-controlled phase 2 trial of zuranolone in adults with major depressive disorder. J. Affect Disord. 308, 19–26. https://doi.org/10.1016/j.jad.2022.03.068.

Svenningsson, P., Nishi, A., Fisone, G., Girault, J.-A., Nairn, A.C., Greengard, P., 2004. DARPP-32: an integrator of neurotransmission. Annu Rev. Pharmacol. Toxicol. 44, 269–296. https://doi.org/10.1146/annurev.pharmtox.44.101802.121415.

Swerdlow, N.R., Braff, D.L., Taaid, N., Geyer, M.A., 1994. Assessing the validity of an animal model of deficient sensorimotor gating in schizophrenic patients. Arch. Gen. Psychiatry 51, 139–154. https://doi.org/10.1001/archpsyc.1994.03950020063007.

Swerdlow, N.R., Karban, B., Ploum, Y., Sharp, R., Geyer, M.A., Eastvold, A., 2001. Tactile prepuff inhibition of startle in children with Tourette's syndrome: in search of an "fMRI-friendly" startle paradigm. Biol. Psychiatry 50, 578–585. https://doi.org/10.1016/s0006-3223(01)01164-7.

Tomaselli, G., Vallée, M., 2019. Stress and drug abuse-related disorders: The promising therapeutic value of neurosteroids focus on pregnenolone-progesterone-allopregnanolone pathway. Front. Neuroendocr. 55, 100789 https://doi.org/10.1016/j.yfrne.2019.100789.

Torres, J.M., Ortega, E., 2003. Differential regulation of steroid 5alpha-reductase isozymes expression by androgens in the adult rat brain. FASEB J. 17, 1428–1433. https://doi.org/10.1096/fj.02-1119com.

Traccis, F., Serra, V., Sagheddu, C., Congiu, M., Saba, P., Giua, G., Devoto, P., Frau, R., Cheer, J.F., Melis, M., 2021. Prenatal THC does not affect female mesolimbic dopaminergic system in preadolescent rats. Int. J. Mol. Sci. 22, 1666. https://doi.org/10.3390/ijms22041666.

Traish, A.M., 2020. Health Risks Associated with Long-Term Finasteride and Dutasteride Use: It's Time to Sound the Alarm. World J. Mens. Health 38, 323–337. https://doi.org/10.5534/wjmh.200012.

Traish, A.M., Haider, K.S., Doros, G., Haider, A., 2015a. Finasteride, not tamsulosin, increases severity of erectile dysfunction and decreases testosterone levels in men with benign prostatic hyperplasia. Horm. Mol. Biol. Clin. Invest. 23, 85–96. https://doi.org/10.1515/hmbci-2015-0015.

Traish, A.M., Melcangi, R.C., Bortolato, M., Garcia-Segura, L.M., Zitzmann, M., 2015b. Adverse effects of 5α-reductase inhibitors: What do we know, don't know, and need to know? Rev. Endocr. Metab. Disord. 16, 177–198. https://doi.org/10.1007/s11154-015-9319-y.

Traish, A.M., Mulgaonkar, A., Giordano, N., 2014. The dark side of 5α-reductase inhibitors' therapy: sexual dysfunction, high Gleason grade prostate cancer and depression. Korean J. Urol. 55, 367–379. https://doi.org/10.4111/kju.2014.55.6.367.

Tronci, E., Napolitano, F., Muñoz, A., Fidalgo, C., Rossi, F., Björklund, A., Usiello, A., Carta, M., 2017. BDNF over-expression induces striatal serotonin fiber sprouting and increases the susceptibility to l-DOPA-induced dyskinesia in 6-OHDA-lesioned rats. Exp. Neurol. 297, 73–81. https://doi.org/10.1016/j.expneurol.2017.07.017.

Vacher, C.-M., Lacaille, H., O'Reilly, J.J., Salzbank, J., Bakalar, D., Sebaoui, S., Liere, P., Clarkson-Paredes, C., Sasaki, T., Sathyanesan, A., Kratimenos, P., Ellegood, J., Lerch, J.P., Imamura, Y., Popratiloff, A., Hashimoto-Torii, K., Gallo, V., Schumacher, M., Penn, A.A., 2021. Placental endocrine function shapes cerebellar development and social behavior. Nat. Neurosci. 24, 1392–1401. https://doi.org/10.1038/s41593-021-00896-4.

Vallée, M., 2016. Neurosteroids and potential therapeutics: Focus on pregnenolone. J. Steroid Biochem Mol. Biol. 160, 78–87. https://doi.org/10.1016/j.jsbmb.2015.09.030.

Vallée, M., Vitiello, S., Bellocchio, L., Hébert-Chatelain, E., Monlezun, S., Martin-Garcia, E., Kasanetz, F., Baillie, G.L., Panin, F., Cathala, A., Roullot-Lacarrière, V., Fabre, S., Hurst, D.P., Lynch, D.L., Shore, D.M., Deroche-Gamonet, V., Spampinato, U., Revest, J.-M., Maldonado, R., Reggio, P.H., Ross, R.A., Marsicano, G., Piazza, P.V., 2014. Pregnenolone can protect the brain from cannabis intoxication. Science 343, 94–98. https://doi.org/10.1126/science.1243985.

Vashchinkina, E., Manner, A.K., Vekovischeva, O., den Hollander, B., Uusi-Oukari, M., Aitta-Aho, T., Korpi, E.R., 2014. Neurosteroid Agonist at GABAA receptor induces persistent neuroplasticity in VTA dopamine neurons. Neuropsychopharmacology 39, 727–737. https://doi.org/10.1038/npp.2013.258.

Viggiano, D., Grammatikopoulos, G., Sadile, A.G., 2002. A morphometric evidence for a hyperfunctioning mesolimbic system in an animal model of ADHD. Behav. Brain Res 130, 181–189. https://doi.org/10.1016/s0166-4328(01)00423-5.

Wang, H., Farhan, M., Xu, J., Lazarovici, P., Zheng, W., 2017. The involvement of DARPP-32 in the pathophysiology of schizophrenia. Oncotarget 8, 53791–53803. https://doi.org/10.18632/oncotarget.17339.

Wang, M., Seippel, L., Purdy, R.H., Bäckström, T., 1996. Relationship between symptom severity and steroid variation in women with premenstrual syndrome: study on serum pregnenolone, pregnenolone sulfate, 5 alpha-pregnane-3,20-dione and 3 alpha-hydroxy-5 alpha-pregnan-20-one. J. Clin. Endocrinol. Metab. 81, 1076–1082. https://doi.org/10.1210/jcem.81.3.8772579.

Weill-Engerer, S., David, J.-P., Sazdovitch, V., Liere, P., Eychenne, B., Pianos, A., Schumacher, M., Delacourte, A., Baulieu, E.-E., Akwa, Y., 2002. Neurosteroid quantification in human brain regions: comparison between Alzheimer's and nondemented patients. J. Clin. Endocrinol. Metab. 87, 5138–5143. https://doi.org/10.1210/jc.2002-020878.

Weintraub, D., Koester, J., Potenza, M.N., Siderowf, A.D., Stacy, M., Voon, V., Whetteckey, J., Wunderlich, G.R., Lang, A.E., 2010. Impulse control disorders in Parkinson disease: a cross-sectional study of 3090 patients. Arch. Neurol. 67, 589–595. https://doi.org/10.1001/archneurol.2010.65.

Weintraub, D., Mamikonyan, E., 2019. The Neuropsychiatry of Parkinson Disease: A Perfect Storm. Am. J. Geriatr. Psychiatry 27, 998–1018. https://doi.org/10.1016/j.jagp.2019.03.002.

Wetten, A., Ogle, L., Mells, G., Hegade, V.S., Jopson, L., Corrigan, M., Palmer, J., Johansson, M., Bäckström, T., Doverskog, M., Jones, D.E.J., Dyson, J.K., 2022. Neurosteroid Activation of GABA-A Receptors: A Potential Treatment Target for Symptoms in Primary Biliary Cholangitis? Can. J. Gastroenterol. Hepatol. 2022, 3618090 https://doi.org/10.1155/2022/3618090.

Wilding, T.J., Lopez, M.N., Huettner, J.E., 2016. Chimeric Glutamate Receptor Subunits Reveal the Transmembrane Domain Is Sufficient for NMDA Receptor Pore Properties but Some Positive Allosteric Modulators Require Additional Domains. J. Neurosci. 36, 8815–8825. https://doi.org/10.1523/JNEUROSCI.0345-16.2016.

Wong, P., Chang, C.C.R., Marx, C.E., Caron, M.G., Wetsel, W.C., Zhang, X., 2012. Pregnenolone rescues schizophrenia-like behavior in dopamine transporter knockout mice. PLoS One 7, e51455. https://doi.org/10.1371/journal.pone.0051455.

Wong, P., Sze, Y., Chang, C.C.R., Lee, J., Zhang, X., 2015. Pregnenolone sulfate normalizes schizophrenia-like behaviors in dopamine transporter knockout mice

through the AKT/GSK3β pathway. Transl. Psychiatry 5, e528. https://doi.org/10.1038/tp.2015.21.
Yoest, K.E., Quigley, J.A., Becker, J.B., 2018. Rapid effects of ovarian hormones in dorsal striatum and nucleus accumbens. Horm. Behav. 104, 119–129. https://doi.org/10.1016/j.yhbeh.2018.04.002.
Zald, D.H., Treadway, M.T., 2017. Reward Processing, Neuroeconomics, and Psychopathology. Annu Rev. Clin. Psychol. 13, 471–495. https://doi.org/10.1146/annurev-clinpsy-032816-044957.