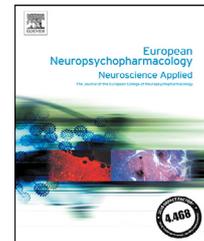www.elsevier.com/locate/euroneuro

REVIEW

Psychotropic and neurological medication effects on mitochondrial complex I and IV in rodent models

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Abstract
Mitochondrial complex I (NADH-dehydrogenase) and complex IV (cytochrome-c-oxidase) are reported to be affected by drugs used to treat psychiatric or neurodegenerative diseases, including antidepressants, antipsychotics, anxiolytics, mood stabilizers, stimulants, antidementia, and antiparkinsonian drugs.
We conducted meta-analyses examining the effects of each drug category on complex I and IV. The electronic databases Pubmed, EMBASE, CENTRAL, and Google Scholar were searched for studies published between 1970 and 2018.
Of 3105 screened studies, 68 articles covering 53 drugs were included in the meta-analyses. All studies assessed complex I and IV in rodent brain at the level of enzyme activity. Results revealed that selected antidepressants increase or decrease complex I and IV, antipsychotics and stimulants decrease complex I but increase complex IV, whereas anxiolytics, mood stabilizers, antidementia, and antiparkinsonian drugs preserve or even enhance both complex I and IV. Potential contributions to the drug effects were found to be related to the drugs' neurotransmitter receptor profiles with adrenergic (α1B), dopaminergic (D1/2), glutaminergic (NMDA1,3),

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histaminergic (H1), muscarinic (M1,3), opioid (OP1-3), serotonergic (5-HT$_{2A}$, 5-HT$_{2C}$, 5-HT$_{3A}$) and sigma (σ1) receptors having the greatest effects.

The findings are discussed in relation to pharmacological mechanisms of action that might have relevance for clinical and research applications.

1. Introduction

Impaired mitochondrial function is linked to the pathophysiology of major psychiatric disorders such as mood disorders and schizophrenia (Bansal and Kuhad, 2016; Hroudová and Fišar, 2011; Kato, 2017) and neurodegenerative disorders such as Alzheimer's and Parkinson's (Onyango et al., 2017). Mitochondrial function is essential for production of adenosine triphosphate (ATP), the main source of cellular energy. Impaired mitochondrial function results in decreased energy metabolism, reduced bioenergetics, oxidative stress, and apoptosis (Hroudová and Fišar, 2011).

Psychotropic medication used to treat psychiatric or neurodegenerative conditions may target mitochondrial dysfunction (Anglin, 2016; Ben-Shachar Dorit, 2002). For instance, psychiatric drugs such as antidepressants are thought to inhibit mitochondrial respiration leading to decreased ATP production in animal models of depression (Adzic et al., 2016). Both typical and atypical antipsychotics impair mitochondrial function by inducing structural gene changes also implicated in depletion of ATP supply (Manatt and Chandra, 2011). Anxiolytics such as benzodiazepines (Neustadt and Pieczenik, 2008) and stimulants such as amphetamines (Brown and Yamamoto, 2003) weaken mitochondrial function through the formation of free radicals, particularly reactive oxygen species. Conversely, mood stabilizers such as lithium or valproic acid have been shown to preserve or even enhance mitochondrial function by increasing the rate of cellular respiration (Manatt and Chandra, 2011). Similarly, medication to treat neurodegenerative disorders, for example antidementia drugs such as cholinesterase inhibitors (ChEIs) or antiparkinsonian drugs such as the dopamine agonist levodopa (Winklhofer and Haass, 2010) or monoamine oxidase inhibitors (MAOIs) (Hroudová et al., 2016), may have neuroprotective effects that restore and maintain mitochondrial function. Together, these effects may contribute to both adverse effects and efficacy of many psychotropic medications, not only in patients with mitochondrial disorders but also in the much wider population receiving these agents for psychiatric or neurodegenerative illnesses (Anglin et al., 2012) as we have discussed in our previous meta-analysis (Holper et al., 2018).

Prior to ATP generation, mitochondria direct electrons extracted from nutrients into a transmembrane proton gradient and this process is mediated by the electron transport chain (ETC). Two enzymes of the ETC located at the inner mitochondrial membrane are the most impaired in psychiatric and neurodegenerative disorders based on our recent meta-analysis (Holper et al., 2018) and the most affected ETC enzymes by psychotropic drugs (Hroudová and Fisar, 2010). The first enzyme, complex I (NADH dehydrogenase, NDU), is one of the entry enzymes of cellular respiration or oxidative phosphorylation in the mitochondrion. NDU is the largest multimeric ETC complex and a major contributor to the proton gradient across the mitochondrial inner membrane, which drives ATP production. The second enzyme of interest, complex IV (cytochrome-c-oxidase, COX), catalyzes the final step in the ETC. Due to its rate-limiting role in this oxidative process (Arnold, 2012) and its coupling with neuronal activation (Wong-Riley, 2012), COX is proposed as a key marker of mitochondrial as well as neuronal function (Srinivasan and Avadhani, 2012). The two enzymes interact in that an assembled complex IV is required to maintain the stability of complex I (Li et al., 2007). Both complex I and IV also represent clinically relevant targets due to their accessibility using novel in-vivo technologies assessing complex I redox states (Blacker and Duchen, 2016) or oxidized complex IV (Bale et al., 2016).

We chose the seven drug categories of antidepressants, antipsychotics, anxiolytics, mood stabilizers, stimulants, antidementia, and antiparkinsonian drugs, not only because of their potential common effects on mitochondrial function, but also based on the overlapping indications for which they are used to treat in clinical practice. Antidepressants are used in mood and anxiety disorders, but are also frequently applied to treat depressive symptomatology in schizophrenia and both Alzheimer's and Parkinson's (Lanctôt et al., 2017; Zhuo et al., 2017). Antipsychotics are used in schizophrenia as well as mood disorders to ameliorate psychotic episodes and used as antidepressants and anti-manic treatment (Correll et al., 2015). Mood stabilizers are typically used for recurrent bipolar disorders and include atypical antipsychotics that may also have anti-aggressive effects (Fazel et al., 2014) and possible improve negative symptoms (Clelland et al., 2016). Anxiolytics and stimulants are commonly given alone or in combination with antidepressants to treat comorbid anxiety (Drobizhev et al., 2015), fatigue, or attention deficits (Malhi et al., 2016). Antidementia drugs are not only used in Alzheimer's to improve cognitive function but also in Parkinson's (O'Brien et al., 2017) and schizophrenia (Kishi et al., 2018) to treat comorbid dementia symptoms.

Besides the overlap in clinical application, the seven drug categories also show similarities in their mechanisms of action and neurotransmitter receptor and transporter binding profiles. Antidepressants, such as selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), or norepinephrine and dopamine reuptake inhibitors (NDRIs), primarily increase the levels of the monoamine neurotransmitters serotonin (5-hydroxytryptamine, 5-HT), norepinephrine, and dopamine (D) by inhibiting their reuptake at the corresponding transporters (SERT, NET, DAT) (Cusack et al., 1994); to a lesser extent, some antidepressants also interact with adrenergic (α,β), glutaminergic (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid, AMPA, N-methyl-D-aspartate,

NMDA), histaminergic (H), muscarinic (M), melatonergic (MT), and sigma (σ) receptors. Typical antipsychotics exert their clinical effects as D2 receptor antagonists as their common target (Mauri et al., 2014) and 5-HT$_{2A}$ receptor antagonists for atypical antipsychotics (Sullivan et al., 2015). Occupancy of other 5-HT receptors and α, H, M receptors contributes to side effects and adverse effects (Scigliano and Ronchetti, 2013). Anxiolytics such as benzodiazepines exert their various effects through allosteric modulation of gamma-aminobutyric acid (GABA-A) receptor (Jensen et al., 2014). Stimulants work by releasing dopamine and also have a moderate affinity for monoamine transporters (SERT, NET, DAT) (Calipari and Ferris, 2013) and to a lesser extent for and D receptors (Banerjee et al., 1978). Similarly, antidementia drugs such as cholinesterase inhibitors (ChEIs) and antiparkinsonian drugs such as the dopamine agonist levodopa target D receptors, inhibit acetylcholine (ACh) catabolism and have down-stream effects on 5-HT, α, DAT and NMDA receptors (Perez-Lloret et al., 2014). These and other receptors have been shown to affect mitochondrial activities and vice versa (Picard et al., 2016).

Numerous excellent reviews (Adzic et al., 2016; Anglin, 2016; Brown and Yamamoto, 2003; Hroudová et al., 2016; Manatt and Chandra, 2011; Neustadt and Pieczenik, 2008; Winklhofer and Haass, 2010) have discussed the detailed effects on complex I and IV caused by each of the above-mentioned drug categories. A meta-analysis summarizing the findings across these drugs could not be found in the literature. We therefore aimed to conduct a literature review, screening for suitable papers and meta-analyzing the effects of each drug category on complex I and IV. The present work thereby aimed to extend our previous meta-analysis focusing on psychiatric and neurodegenerative disease levels (Holper et al., 2018).

2. Experimental procedures

2.1. Literature search and study identification

We conducted a structured literature search in PubMed, EMBASE, CENTRAL, and Google Scholar to identify studies published between January 1970 and May 2018 using the search strings 'NADH dehydrogenase' OR 'cytochrome-c-oxidase' OR 'complex I' OR 'complex IV' AND 'antidepressants' OR 'antipsychotics' OR 'anxiolytics' OR 'mood stabilizers' OR 'stimulants' OR 'Alzheimer' OR 'Parkinson'. We additionally manually reviewed reference lists in all retrieved articles for related publications. Inclusion criteria were: studies published in the English language, studies investigated complex I and/or complex IV, studies reporting data in rodent disease models in comparison with a control group. Exclusion criteria were: studies in human patient populations, studies in other tissues than brain tissue, cellular studies, genetic studies, case reports, and publications not reporting original data.

2.2. Data extraction

Aggregated data were extracted for each of the seven drugs categories: antidepressants, antipsychotics, anxiolytics, mood stabilizers, stimulants, antidementia, and antiparkinsonian drugs. Aggregated data contained qualitative information (i.e., drug names, drug mechanisms of action, and brain regions of interest (ROIs)),

quantitative data (i.e., number of drug-administered and control animals, age, sex, strain, enzyme measurements, dosage and duration of drug administration, and potential disease models), and outcomes (effect sizes in terms of standardized mean differences (SMD) and p-values). In case of aggregated data not presented in the text, the authors were contacted for permission to reuse original data or data were read from figures. Mechanisms of action, receptor affinity profiles and lipophilicity values (logP) of each drugs were derived from DrugBank (Wishart et al., 2018), when available.

2.3. Multivariate random-effect meta-analyses

Three separate meta-analyses were computed for complex I and IV separately to estimate: (1) the effects of drugs; (2) the effects of mechanisms of action; and (3) the effects of receptor affinity.

Moderators were built for each meta-analysis. 'Drug' moderators were based on the International Nonproprietary Names (INN) of the corresponding active pharmaceutical ingredients (e.g., 'escitalopram' for cipralex). 'Mechanism of action' moderators were built by categorizing each drug according to its corresponding primary drug mechanism (e.g., 'escitalopram' was categorized as 'SSRI'); drugs with unknown mechanisms of action were categorized according to their therapeutic uses (e.g., 'valproic acid' was categorized as 'antiepileptic drug (AEG)'). 'Receptor affinity' moderators were built by assigning each drug to its corresponding affinity for one or more of the various neurotransmitter receptors, transporters, or enzymes (Wishart et al., 2018), if available. The type of receptor binding, i.e., agonism or antagonism (coded 1 and −1), was treated as a covariate. Not considered was binding affinity (i.e., the inhibitory constant, Ki), since it is not available for all drugs. 'Lipophilicity' moderators were built by assigning each drug to its corresponding lipophilicity value (logP) (Wishart et al., 2018). Additional sensitivity analyses were conducted to assess the effects of potential confounding covariates age (Navailles et al., 2008; Olivares-Nazario et al., 2015), sex (Kreiner et al., 2013), strain (Lucki et al., 2001; Ripoll et al., 2003), measurement type, and disease model.

All meta-analyses were performed using a multivariate, random-effect model based on the Metafor package (Viechtbauer, 2010) as implemented in R (R Development Core Team, 2008). The multivariate model accounted for heterogeneity and dependency in the underlying true effects of multiple moderators that could overlap within subjects and studies (random factors). To adjust for dosage (mg/day) and administration duration (days) of the specific drugs, categorical dummy covariates were used. To adjust for sample size, effects were weighted based on study size. To allow for heterogeneity differences between moderators, an unstructured variance-covariance matrix was applied (function rma.mv; observed effects = SMD + dosage + duration; variance-covariance matrix = COV; weight = study size; variance structure = UN; moderators = 'drugs' OR 'mechanism of action' OR 'receptor affinity: type'; random factors = subject + study; method = REML). A Wald-type test (Viechtbauer, 2010) was used to compare subgroup estimates between complex I and IV.

Heterogeneity was assessed using Cochran's Q-test and the inconsistency I^2 statistic that directly indicates to what extent each outcome contributes to the total variance. Publication bias was assessed using Egger's regression analysis.

3. Results

3.1. Data extraction

Of 3105 screened studies, 68 studies were eligible for the meta-analyses (Table 1, Dataset S1) on antidepressants

Table 1 Eligible studies. 68 studies were eligible for the meta-analyses covering 53 drugs. Mechanisms of actions are indicated (Wishart et al., 2018). Some studies reported more than one drug. The detailed data extracted from these studies are provided in *Dataset S1 and S2*. Antipsychotics (APs), antiepileptic drugs (AEGs), cholinesterase inhibitors (ChEIs), dopamine agonists (DAGs), dopamine reuptake inhibitors (DRIs), gamma-aminobutyric acid (GABA)A receptor positive allosteric modulators (PAMs), monoamine oxidase inhibitors (MAOIs), muscarinic M1 agonists (M1 AGs), N-methyl-D-aspartate receptor antagonists (NMDA ANTs), noradrenergic and specific serotonergic antidepressants (NaSSAs), norepinephrine-dopamine disinhibitors (NDDIs), norepinephrine–dopamine reuptake inhibitors (NDRIs), norepinephrine reuptake inhibitors (NRIs), reversible inhibitors of monoamine oxidase A (RIMAs), serotonin antagonist and reuptake inhibitors (SARIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), selective serotonin reuptake enhancers (SSREs), selective serotonin reuptake inhibitors (SSRIs).

Antidepressants	Complex	Mechanism	References
Agomelatine	I, IV	NDDI	Gupta and Sharma (2014), Kumar et al. (2015), Singh and Kumar (2015), de Mello et al. (2015)
Amitriptyline	I, IV	NRI	González-Pardo et al. (2008), Hroudová and Fisar (2010)
Bupropion	I, IV	NDRI	Ferreira et al. (2012)
Citalopram	I, IV	SSRI	Hroudová and Fisar (2010)
Desipramine	I, IV	NRI	Hroudová and Fisar (2010), Villa et al. (2017)
Escitalopram	I, IV	SSRI	Gonçalves et al. (2012)
Fluoxetine	I, IV	SSRI	Adzic et al. (2013), Padilla et al. (2011), Shumake et al. (2010), Villa et al. (2017)
Fluvoxamine	I, IV	SSRI	Ferreira et al. (2014)
Imipramine	I, IV	SNRI	Abelaira et al. (2011), Della et al. (2012), Hroudová and Fisar (2010), Ignácio et al. (2015), Kumar et al. (2010), Réus et al. (2012)
Ketamine	I, IV	NMDA ANT	Rezin et al. (2009, 2010), Réus et al. (2015), Venâncio et al. (2015), de Oliveira et al. (2011)
Mirtazapine	I, IV	NaSSA	Hroudová and Fisar (2010)
Moclobemide	I, IV	RIMA	Hroudová and Fisar (2010)
Nortriptyline	I, IV	NRI	Scaini et al. (2011)
Paroxetine	I, IV	SSRI	Garabadu et al. (2015), Scaini et al. (2011)
Sertraline	I, IV	SSRI	Gaur and Kumar (2010), Kumar et al. (2010), Sharma et al. (2016)
Tianeptine	I, IV	SSRE	Della et al. (2012, 2013), Hroudová and Fisar (2010)
Trazodone	I, IV	SARI	Kumar et al. (2010)
Venlafaxine	I, IV	SNRI	Hroudová and Fisar (2010), Kumar et al. (2010), Scaini et al. (2011), Sharma et al. (2016)
Antipsychotics	**Complex**	**Mechanism**	**References**
Aripiprazole	I, IV	Atypical AP	Scaini et al. (2013), Streck et al. (2007)
Chlorpromazine	I, IV	Typical AP	Balijepalli et al. (1999), Burkhardt et al. (1993)
Clozapine	I, IV	Atypical AP	Balijepalli et al. (1999, 2001), Burkhardt et al. (1993), Prince et al. (1997, 1998), Przedborski et al. (1995), Scaini et al. (2013), Streck et al. (2007)
Fluphenazine	I, IV	Typical AP	Balijepalli et al. (1999), Prince et al. (1997, 1998)
Haloperidol	I, IV	Typical AP	Balijepalli et al. (1999, 2001), Barrientos et al. (1998), Burkhardt et al. (1993), Prince et al. (1997, 1998), Streck et al. (2007)
Molindone	I	Typical AP	Przedborski et al. (1995)
Olanzapine	I, IV	Atypical AP	Hroudová and Fisar (2010), Scaini et al. (2013), Streck et al. (2007)
Quetiapine	I, IV	Atypical AP	Ignácio et al. (2015)
Risperidone	I, IV	Atypical AP	Balijepalli et al. (1999, 2001), Garabadu et al. (2015)
Thiothixene	I, IV	Typical AP	Burkhardt et al. (1993)
Anxiolytics	**Complex**	**Mechanism**	**References**
Clonazepam	I, IV	GABA-A PAM	Mohamed et al. (2013)
Diazepam	I, IV	GABA-A PAM	Kumar et al. (2014), van der Kooij et al. (2018)
Mood stabilizers	**Complex**	**Mechanism**	**References**
Gabapentin	I, IV	AEG	Kumar et al. (2012, 2014)
Lamotrigine	I, IV	AEG	Abelaira et al. (2011), Kumar et al. (2012)
Lithium	I, IV	Lithium	Bachmann et al. (2009), Feier et al. (2013), Hroudová and Fisar (2010), Kim et al. (2016), Lambert et al. (1999), Tan et al. (2012), Valvassori et al. (2010)
Topiramate	I, IV	AEG	Kudin et al. (2004)
Valproic acid	I, IV	AEG	Bachmann et al. (2009), Feier et al. (2013), Hroudová and Fisar (2010), Mishra et al. (2014), Valvassori et al. (2010)

Table 1   (*continued*)

Stimulants	Complex	Mechanism	References
Amphetamine	I	DRI	Tan et al. (2012)
Mazindol	I, IV	DRI	Gonçalves et al. (2014)
Methamphetamine	I, IV	DRI	Brown et al. (2005), Killinger et al. (2014), Thrash et al. (2010), Thrash-Williams et al. (2013, 2016)
Methylphenidate	I, IV	DRI	Fagundes et al. (2007, 2010)
Antidementia	**Complex**	**Mechanism**	**References**
7-MEOTA	I, IV	Unknown	Singh et al. (2017)
Donepezil	I, IV	ChEI	Singh and Kumar (2015), Singh et al. (2017)
Galantamine	I, IV	ChEI	Singh et al. (2015, 2017)
Latrepirdine	I, IV	Unknown	Singh et al. (2017)
Memantine	I, IV	NMDA ANT	Kumar and Sharma (2016), Réus et al. (2012), Singh et al. (2017)
Piracetam	I, IV	Unknown	Singh et al. (2017)
Rivastigmine	I, IV	ChEI	Kumar and Kumar (2009), Singh et al. (2017)
Antiparkinsonian	**Complex**	**Mechanism**	**References**
Amantadine	I	Unknown	Thrash-Williams et al. (2013)
Bromocriptine	I	DAG	Przedborski et al. (1995)
Levodopa	I, IV	DAG	Abdin and Hamouda (2008), Calabrese Vittorio et al. (2007), Dixit et al. (2013), Przedborski et al. (1993), Sharma et al. (2016)
Minocycline	I	Unknown	Dixit et al. (2013)
Pergolide	I	DAG	Przedborski et al. (1995)
Selegiline	I, IV	MAOI	Czerniczyniec et al. (2006), Przedborski et al. (1995), Saravanan et al. (2006)
Trihexyphenidyl	I	M1 AG	Przedborski et al. (1995)

(AD), antipsychotics (AP), anxiolytics (AX), mood stabilizers (MS), stimulants (ST), antidementia drugs (ADD), and antiparkinsonian drugs (APD). In total, studies covered 53 drugs (AD $N = 18$, AP $N = 10$, AX $N = 3$, MS $N = 5$, ST $N = 4$, ADD $N = 7$, APD $N = 7$). The number of studies reporting on complex I (total $N = 72$, AD $N = 24$, AP $N = 10$, AX $N = 4$, MS $N = 10$, ST $N = 9$, ADD $N = 6$, APD $N = 9$) and complex IV (total $N = 62$, AD $N = 26$, AP $N = 9$, AX $N = 3$, MS $N = 10$, ST $N = 6$, ADD $N = 5$, APD $N = 3$) varied between drug categories, some of them reporting the same drug in more than one drug category. Almost all (95%) of the studies used in-vivo drug administration in rodents (Wistar rats 58.3%, Sprague-Dawley rats 20.6%, Swiss mice 5.2%, Holtzman rats 3.4%, CD1 mice 3.1%, Charles Foster rats 2.6%, Laca mice 0.9%, C57BL/6 mice 0.3%, C57/Bl6 mice 0.3%, Fisher CDF rats 0.08%, unknown 5.1%) and analysed complex I and IV at the level of enzymatic activity in the brain tissue after decapitation; and 5% of studies were in-vitro studies using isolated mitochondria. Rodent ages ranged from 0.1-4 months (mean 2.7 months). Rodent sex was 91% male, 4% female, 1% both sexes, and 4% unspecified. 87% of the studies used naïve rodent models, 12% induced chronic mild stress, and 1% of the studies employed a Parkinson's disease model. No eligible studies were found in healthy human brain tissue.

98% of the studies measured enzyme activities using spectrophotometry and expressed results as enzyme activity per milligram of total protein [μmol min^{-1} mg^{-1}] (Cassina and Radi, 1996; Rustin et al., 1994). Only 2% applied western blot. Complex I and IV were analysed either in selected ROIs (AD $N = 24$, AP $N = 7$, AX $N = 2$, MS $N = 9$, ST $N = 8$, ADD $N = 4$, APD $N = 7$) and/or in brain homogenates (AD $N = 14$, AP $N = 9$, AX $N = 2$, MS $N = 3$, ST $N = 5$, ADD $N = 4$, APD $N = 2$). Drugs were investigated in one/two or more dosage

steps (AD $N = 18/10$, AP $N = 6/6$, AX $N = 3/1$, MS $N = 9/2$, ST $N = 5/4$, ADD $N = 4/2$, APD $N = 8/1$). Mean (range) duration of drug administration was similar between drug categories (AD $= 11$ (1-28) days; AP $= 17$ (1-90) days; AX $= 12$ (1-30) days; MS $= 14$ (1-42) days; ST $= 12$ (1-28) days; ADD $= 9$ (1-21) days; APD $= 5$ (1-60) days). Mean number of animals per study (i.e., sum of drug-administered animals plus control animals) was also similar between drug categories (AD $N = 14$, AP $N = 11$, AX $N = 21$, MS $N = 13$, ST $N = 13$, ADD $N = 15$, APD $N = 11$). Control animals received saline or were sham groups in diseases models. Considering all above-mentioned factors, drug category, enzymes, selected ROIs, dosage, and administration duration, 1215 data points were extracted. Mechanisms of action and receptor affinity profiles collected based on previous work (Wishart et al., 2018) are provided in Table 1, Fig. S1, Dataset S2.

3.2. Multivariate random-effect meta-analyses

Meta-analyses assessed complex I and IV enzyme activity regarding the (1) effects of drugs (Fig. 1), (2) effects of mechanisms of action (Fig. 2, top), and (3) effects of receptor affinity (Fig. 2, bottom).

3.2.1. Drugs
Antidepressants had negative effects on complex I for desipramine ($p = 0.026$) and escitalopram ($p < 0.0001$), whereas positive effects were observed for agomelatine ($p = 0.00,017$), paroxetine ($p = 0.034$), and sertraline ($p < 0.0001$) consistent with decreased versus increased NDU enzyme activity. Negative effects on complex IV were found for amitriptyline ($p = 0.023$), desipramine
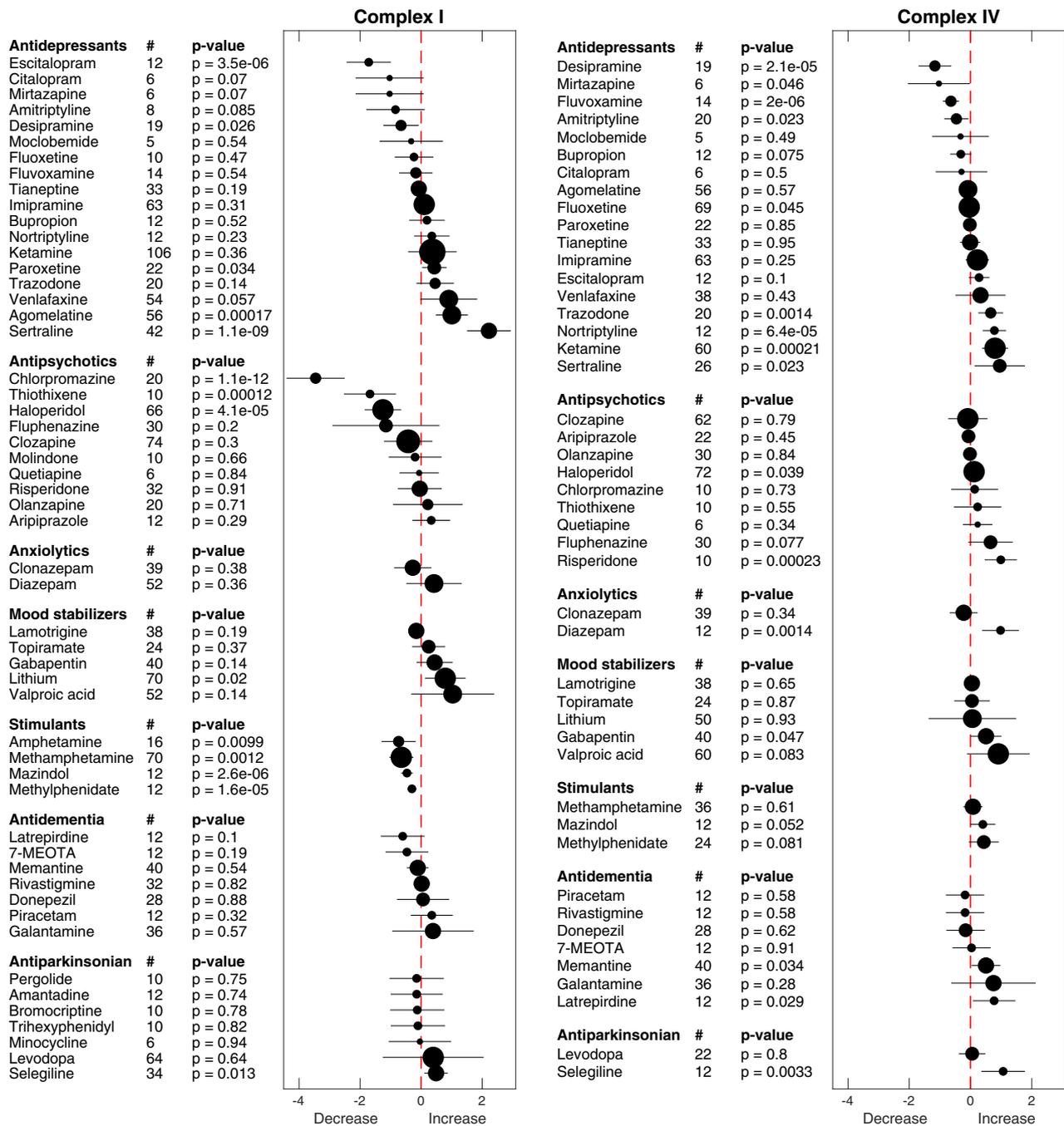
Complex I

Antidepressants	#	p-value
Escitalopram	12	p = 3.5e-06
Citalopram	6	p = 0.07
Mirtazapine	6	p = 0.07
Amitriptyline	8	p = 0.085
Desipramine	19	p = 0.026
Moclobemide	5	p = 0.54
Fluoxetine	10	p = 0.47
Fluvoxamine	14	p = 0.54
Tianeptine	33	p = 0.19
Imipramine	63	p = 0.31
Bupropion	12	p = 0.52
Nortriptyline	12	p = 0.23
Ketamine	106	p = 0.36
Paroxetine	22	p = 0.034
Trazodone	20	p = 0.14
Venlafaxine	54	p = 0.057
Agomelatine	56	p = 0.00017
Sertraline	42	p = 1.1e-09

Antipsychotics	#	p-value
Chlorpromazine	20	p = 1.1e-12
Thiothixene	10	p = 0.00012
Haloperidol	66	p = 4.1e-05
Fluphenazine	30	p = 0.2
Clozapine	74	p = 0.3
Molindone	10	p = 0.66
Quetiapine	6	p = 0.84
Risperidone	32	p = 0.91
Olanzapine	20	p = 0.71
Aripiprazole	12	p = 0.29

Anxiolytics	#	p-value
Clonazepam	39	p = 0.38
Diazepam	52	p = 0.36

Mood stabilizers	#	p-value
Lamotrigine	38	p = 0.19
Topiramate	24	p = 0.37
Gabapentin	40	p = 0.14
Lithium	70	p = 0.02
Valproic acid	52	p = 0.14

Stimulants	#	p-value
Amphetamine	16	p = 0.0099
Methamphetamine	70	p = 0.0012
Mazindol	12	p = 2.6e-06
Methylphenidate	12	p = 1.6e-05

Antidementia	#	p-value
Latrepirdine	12	p = 0.1
7-MEOTA	12	p = 0.19
Memantine	40	p = 0.54
Rivastigmine	32	p = 0.82
Donepezil	28	p = 0.88
Piracetam	12	p = 0.32
Galantamine	36	p = 0.57

Antiparkinsonian	#	p-value
Pergolide	10	p = 0.75
Amantadine	12	p = 0.74
Bromocriptine	10	p = 0.78
Trihexyphenidyl	10	p = 0.82
Minocycline	6	p = 0.94
Levodopa	64	p = 0.64
Selegiline	34	p = 0.013

(x-axis: -4, -2, 0, 2; Decrease — Increase)

Complex IV

Antidepressants	#	p-value
Desipramine	19	p = 2.1e-05
Mirtazapine	6	p = 0.046
Fluvoxamine	14	p = 2e-06
Amitriptyline	20	p = 0.023
Moclobemide	5	p = 0.49
Bupropion	12	p = 0.075
Citalopram	6	p = 0.5
Agomelatine	56	p = 0.57
Fluoxetine	69	p = 0.045
Paroxetine	22	p = 0.85
Tianeptine	33	p = 0.95
Imipramine	63	p = 0.25
Escitalopram	12	p = 0.1
Venlafaxine	38	p = 0.43
Trazodone	20	p = 0.0014
Nortriptyline	12	p = 6.4e-05
Ketamine	60	p = 0.00021
Sertraline	26	p = 0.023

Antipsychotics	#	p-value
Clozapine	62	p = 0.79
Aripiprazole	22	p = 0.45
Olanzapine	30	p = 0.84
Haloperidol	72	p = 0.039
Chlorpromazine	10	p = 0.73
Thiothixene	10	p = 0.55
Quetiapine	6	p = 0.34
Fluphenazine	30	p = 0.077
Risperidone	10	p = 0.00023

Anxiolytics	#	p-value
Clonazepam	39	p = 0.34
Diazepam	12	p = 0.0014

Mood stabilizers	#	p-value
Lamotrigine	38	p = 0.65
Topiramate	24	p = 0.87
Lithium	50	p = 0.93
Gabapentin	40	p = 0.047
Valproic acid	60	p = 0.083

Stimulants	#	p-value
Methamphetamine	36	p = 0.61
Mazindol	12	p = 0.052
Methylphenidate	24	p = 0.081

Antidementia	#	p-value
Piracetam	12	p = 0.58
Rivastigmine	12	p = 0.58
Donepezil	28	p = 0.62
7-MEOTA	12	p = 0.91
Memantine	40	p = 0.034
Galantamine	36	p = 0.28
Latrepirdine	12	p = 0.029

Antiparkinsonian	#	p-value
Levodopa	22	p = 0.8
Selegiline	12	p = 0.0033

(x-axis: -4, -2, 0, 2; Decrease — Increase)

Fig. 1 Forest plot: Drugs. Multivariate estimates of the effects (SMD, 95% CI, *p*-values) of antidepressants, antipsychotics, anxiolytics, mood stabilizers, stimulants, antidementia drugs and antiparkinsonian drugs on complex I and IV enzyme activities. Values lower than 0 indicate that treated animals had lower levels than controls, and vice versa for values greater than 0; the dashed vertical line at SMD = 0 indicates no effect. The size of the filled circles for each estimated SMD is proportional to the weight of the studies.

($p < 0.0001$), fluoxetine ($p = 0.045$), fluvoxamine ($p < 0.0001$) and mirtazapine ($p = 0.046$), whereas positive effects were observed for ketamine ($p = 0.00,021$), nortriptyline ($p < 0.0001$), trazodone ($p = 0.0014$), and sertraline ($p = 0.023$). Differences in drug effects between complex I and IV were observed for agomelatine ($p = 0.0003$), escitalopram ($p < 0.0001$), paroxetine ($p = 0.048$), and sertraline ($p = 0.023$) as assessed using a Wild-type test.

Antipsychotics that had negative effects on complex I included chlorpromazine ($p < 0.0001$), thiothixene ($p = 0.00012$), and haloperidol ($p < 0.0001$) consistent with decreased NDU enzyme activity. By contrast, positive effects on complex IV were observed for haloperidol ($p = 0.039$) and risperidone ($p = 0.00,023$) indicating increased COX enzyme activity. All drug effects were significantly different between complex I and IV (chlorpromazine
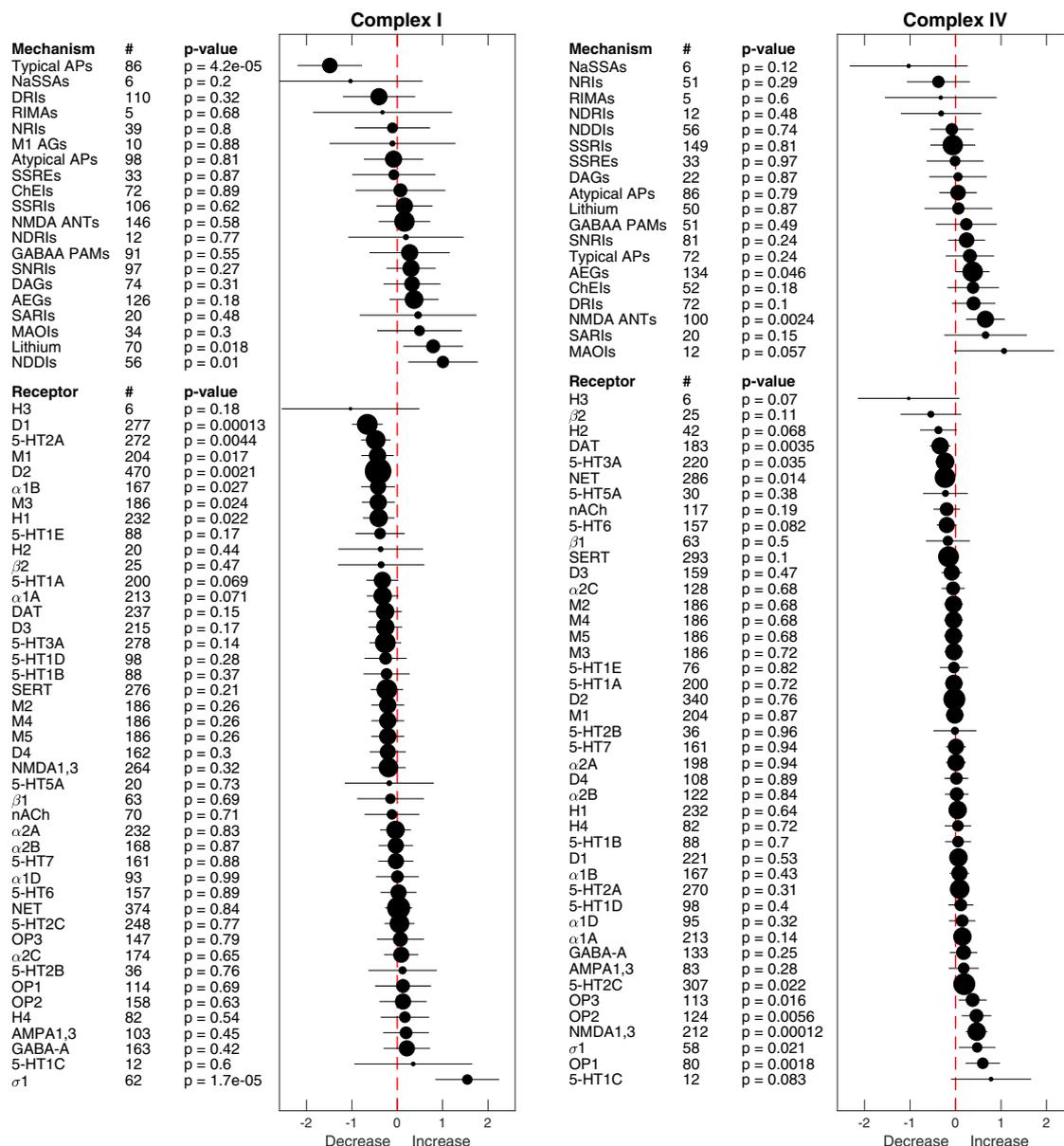
Fig. 2 Forest plot (Top): Mechanism of action. Multivariate estimates of the effects (SMD, 95% CI, *p*-values) on complex I and IV enzyme activities of mechanisms of action* of antidepressants, antipsychotics, anxiolytics, mood stabilizers, stimulants, antidementia drugs and antiparkinsonian drugs.

Forest Plot (Bottom): Receptor affinity. Multivariate estimates of the effects (SMD, 95% CI, *p*-values) on complex I and IV enzyme activities by receptor affinity** of antidepressants, antipsychotics, anxiolytics, mood stabilizers, stimulants, antidementia drugs and antiparkinsonian drugs. Values lower than 0 indicate that animals treated had lower levels than controls, and vice versa for values greater than 0; the dashed vertical line at SMD = 0 indicates no effect. The size of the filled circles for each estimated SMD is proportional to the weight of the studies. See Fig. S1 for drugs affinity profiles.

* Antipsychotics (APs), antiepileptic drugs (AEGs), cholinesterase inhibitors (ChEIs), dopamine agonists (DAGs), dopamine reuptake inhibitors (DRIs), gamma-aminobutyric acid (GABA)A receptor positive allosteric modulators (PAMs), monoamine oxidase inhibitors (MAOIs), muscarinic M1 agonists (M1 AGs), N-methyl-D-aspartate receptor antagonists (NMDA ANTs), noradrenergic and specific serotonergic antidepressants (NaSSAs), norepinephrine-dopamine disinhibitors (NDDIs), norepinephrine–dopamine reuptake inhibitors (NDRIs), norepinephrine reuptake inhibitors (NRIs), reversible inhibitors of monoamine oxidase A (RIMAs), serotonin antagonist and reuptake inhibitors (SARIs), serotonin–norepinephrine reuptake inhibitors (SNRIs), selective serotonin reuptake enhancers (SSREs), selective serotonin reuptake inhibitors (SSRIs).

** Adrenergic (α,β), dopaminergic (D), GABAergic (GABA-A), glutaminergic (NMDA, AMPA), histaminergic (H), muscarinic (M), nicotinic (nACh), opioid (OP), serotonergic (5-HT), sigma (σ). DAT, NET and SERT correspond to the abilities of the drugs to inhibit the reuptake of dopamine, norepinephrine and serotonin, respectively. For details on the receptor type (antagonist or agonist see Table S2).

$p < 0.0001$, haloperidol $p < 0.0001$, risperidone $p = 0.023$, thiothixene $p = 0.001$) as assessed using a Wild-type test.

Anxiolytics had a positive effect on complex IV for diazepam ($p = 0.0014$), and no detectable effects were found on complex I.

Mood stabilizers had a positive effect on complex I for lithium ($p = 0.02$) and on complex IV for gabapentin ($p = 0.047$).

Stimulants having negative effects on complex I included amphetamine ($p = 0.0099$), mazindol ($p < 0.0001$), methamphetamine ($p = 0.0012$), and methylphenidate ($p < 0.0001$). There were no significant effects on complex IV.

Antidementia drugs having positive effects on complex IV included memantine ($p = 0.034$) and latrepirdine ($p = 0.029$). There were no significant effects on complex I.

Antiparkinsonian drugs having a positive effects on both complex I and complex IV were limited to selegiline ($p = 0.013$ and $p = 0.0033$, respectively), without significant differences between complex I and IV effects.

Additional sensitivity analyses showed that the effects on complex I and complex IV were not significantly affected by any of the covariates age, sex, strain, measurement type, or disease model (Table S1).

3.2.2. Mechanisms of action

Categorizing drugs according to their mechanisms of action revealed only few relevant findings compared to the abovementioned analysis. Negative effects on complex I were observed for typical antipsychotics ($p < 0.0001$; Wild-type test $p < 0.0001$), whereas lithium ($p = 0.018$) and NDDIs ($p = 0.01$; Wild-type test $p = 0.025$) had positive effects. Positive effects on complex IV were also found for both AEGs ($p = 0.046$) and NMDA antagonists ($p = 0.0024$) (Fig. 2, top).

3.2.3. Receptor affinity

Receptor affinity profiles were available for 45 drugs (Wishart et al., 2018) (out of 56 drugs) (antidepressants $N = 17$ (out of 18 drugs), antipsychotics $N = 10$ (out of 10 drugs), anxiolytics $N = 2$ (out of 3 drugs), mood stabilizers $N = 4$ (out of 5 drugs), stimulants $N = 4$ (out of 4 drugs), antidementia drugs $N = 4$ (out of 7 drugs), antiparkinsonian drugs $N = 4$ (out of 7 drugs)) (Fig. S1, Dataset S2). The results shown in Fig. 2 (Bottom) thus represent information derived from combinations of drugs that share high affinity for a specific receptor but may differ in their affinity for other receptors.

For complex I, negative effects were found for 5-HT$_{2A}$ ($p = 0.0044$), α1B ($p = 0.027$), D1 ($p = 0.00,013$), D2 ($p = 0.0021$), H1 ($p = 0.022$), M1 ($p = 0.017$), and M3 ($p = 0.024$), whereas positive effects were observed for σ1 ($p < 0.0001$). For complex IV, negative effects were found for 5-HT$_{3A}$ ($p = 0.035$), DAT ($p = 0.0035$), and NET ($p = 0.014$), whereas positive effects were observed for 5-HT$_{2C}$ ($p = 0.022$), NMDA1,3 ($p = 0.00,012$), OP1 ($p = 0.0018$), OP2 ($p = 0.0056$), OP3 ($p = 0.016$), and σ1 ($p = 0.021$). Differences in receptor effects on complex I and IV were found for 5-HT$_{2A}$ ($p = 0.003$), α1A ($p = 0.021$), α1B ($p = 0.021$), D1 ($p = 0.0002$), D2 ($p = 0.014$), H1 ($p = 0.026$), M1 ($p = 0.045$), NMDA1,3 ($p = 0.003$), and σ1 ($p = 0.009$) as assessed using a Wild-type test.

None of abovementioned meta-analyses revealed relevant interaction effects with selected ROIs and we therefore

Table 2 Heterogeneitgooy and Inconsistency. Significant Q statistics indicate the existence of heterogeneity. A I^2 value of 0% indicates no observed inconsistency, whereas larger values shows increasing inconsistency. Egger's regression test for publication bias. The existence of potential publication bias is indicated by p-values < 0.05. df = degrees of freedom.

Heterogeneity and inconsistency

		Q	p-value	I^2 (%)
Complex I	Antidepressants	682.00	0.000	86%
	Antipsychotics	533.87	0.000	87%
	Anxiolytics	34.99	0.000	89%
	Mood stabilizers	131.09	0.000	85%
	Stimulants	45.93	0.434	11%
	Antidementia drugs	122.33	0.000	71%
	Antiparkinsonian drugs	83.39	0.000	84%
Complex IV	Antidepressants	707.35	0.000	71%
	Antipsychotics	661.47	0.000	76%
	Anxiolytics	4.57	0.102	87%
	Mood stabilizers	339.63	0.000	80%
	Stimulants	111.71	0.000	53%
	Antidementia drugs	57.39	0.000	63%
	Antiparkinsonian drugs	5.58	0.589	34%

Egger's regression

		z-value	df	p-value
Complex I	Antidepressants	1.74	22	0.095
	Antipsychotics	−1.36	8	0.211
	Anxiolytics	0.49	2	0.671
	Mood stabilizers	1.54	8	0.161
	Stimulants	−0.13	7	0.902
	Antidementia drugs	−1.16	4	0.311
	Antiparkinsonian drugs	1.23	7	0.258
Complex IV	Antidepressants	0.44	24	0.665
	Antipsychotics	0.23	7	0.822
	Anxiolytics	3·73	1	0.167
	Mood stabilizers	1.10	8	0.302
	Stimulants	0.64	4	0.558
	Antidementia drugs	−0.07	3	0.949
	Antiparkinsonian drugs	0.97	1	0.511

do not report the corresponding results. Lipophilicity revealed no significant effects on complex I or complex IV for any of the drug subgroups or across all drugs ($p > 0.05$).

3.3. Heterogeneity and publication bias

Overall, there was a high degree of heterogeneity as indicated by significant Q-statistics ($p < 0.05$) and large I^2 values (Table 2). Putative low heterogeneity was observed for stimulants in complex I ($Q = 45·93$, $p = 0.434$, $I^2 = 11\%$), anxiolytics in complex IV ($Q = 4·57$, $p = 0.102$, $I^2 = 82\%$), and antiparkinsonian drugs in complex IV ($Q = 5·58$, $p = 0.589$, $I^2 = 34\%$), perhaps explained by the small study numbers in those drug categories (Table 1). Publication bias as assessed using Egger's regression test (Table 2) revealed non-significant results for all drug categories indicating no relevant publication bias.

4. Discussion

This meta-analysis finds many drugs used to treat psychiatric and neurodegenerative disorders to affect mitochondrial complex I and IV. Overall antidepressants show the most heterogenous effects on complex I and IV with some exhibiting negative effects while others have positive effects. Antipsychotics and stimulants primarily decrease complex I but increase complex IV. By contrast, anxiolytics, mood stabilizers, antidementia, and antiparkinsonian drugs affect both complex I and IV positively. To narrow down potential contributors to the drug effects, we meta-analysed mechanisms of action and receptor profiles and found that antagonism of adrenergic (α1B), dopaminergic (D1,2), histaminergic (H1), muscarinic (M1,3) and serotonergic (5-HT$_{2A}$) receptors result in negative effects on complex I, whereas agonism of sigma (σ1) receptors increases complex I. By contrast, antagonism of serotonergic (5-HT$_{3A}$) receptors as well as inhibition of DAT and NET are associated with decreases in complex IV, whereas antagonism of glutaminergic (NMDA1,3) and serotonergic (5-HT$_{2C}$) receptors as well as agonism of opioid (OP1-3) and sigma (σ1) receptors results in positive effects on complex IV. These findings support a relationship between drug effects and receptor affinity profiles and mitochondrial complex I and IV, which may have relevance for selection of treatment with low mitochondrial toxic potential in psychiatric and neurodegenerative conditions as we have discussed in our previous meta-analysis focusing on psychiatric and neurodegenerative disease levels (Holper et al., 2018).

4.1. Antidepressants

Antidepressants have heterogenous effects on complex I and IV independent of their canonical mechanisms of action (Figs. 1 and 2). For example, while some SSRIs exhibit negative effects such as escitalopram on complex I (Gonçalves et al., 2012) or fluoxetine and fluvoxamine on complex IV (Adzic et al., 2013; Ferreira et al., 2014; Padilla et al., 2011; Shumake et al., 2010; Villa et al., 2017), other SSRIs have positive effects such as paroxetine on complex I (Garabadu et al., 2015; Scaini et al., 2011) and sertraline on both complex I and IV (Gaur and Kumar, 2010; Kumar et al., 2010). Similarly, some norepinephrine reuptake inhibitors (NRIs) such as desipramine and amitriptyline reveal strong negative effects on complex I and/or IV (González-Pardo et al., 2008; Hroudová and Fisar, 2010; Villa et al., 2017), whereas nortriptyline, another NRI, affects complex IV positively (Scaini et al., 2011). Noradrenergic and specific serotonergic antidepressants (NaSSAs) such as mirtazapine have negative effects on complex IV (and I) (Hroudová and Fisar, 2010), while serotonin antagonists and reuptake inhibitors (SARIs) such as trazodone were observed to have a positive effect on complex IV (Kumar et al., 2010). The heterogeneity of these effects is likely related to the broader receptor profile of antidepressants such as antagonizing or agonizing adrenergic, dopaminergic, histaminergic, muscarinic, opioid, serotonergic and sigma receptors and inhibiting DAT, NET and SERT transporters. The combination of those receptor profiles in different antidepressants may lead to opposite effects on complex I and IV (Fig. 2,

bottom). For example, antagonism of most serotonergic, i.e., 5-HT$_{1A}$, 5-HT$_{2A/C}$, 5-HT$_3$, receptors has previously been shown to inhibit complex I, mitochondrial biogenesis and oxidative metabolism in rodent hippocampal neurons (Chen et al., 2007), kidney (Harmon et al., 2016), and cardiac mitochondria (Wang et al., 2016), respectively, in line with our findings (Fig. 2, bottom). Similarly, antagonism of muscarinic (M) (De Sarno et al., 2003) and histaminergic, especially H3 brain-specific receptors (Fernandez-Novoa, 2016), inhibits natural mitochondrial protection from apoptotic and oxidative stress, the latter potentially antagonizing neuroprotective NMDA receptor activation (Hansen et al., 2010). Likewise, antagonism of adrenergic α (Beak et al., 2017) and β (Cameron et al., 2017) receptors can inhibit mitochondrial function by blocking their role in the stimulation of mitochondrial biogenesis (Fig. 2, bottom). By contrast, opioid receptors, especially delta-opioid receptors (OP1) (Fig. 2, bottom), are neuroprotective, particularly in cerebral cortex, by stabilizing ionic homeostasis, increasing antioxidant capacity and attenuating disrupted neuronal transmission (Guo, 2015). Also, sigma (σ) receptor agonism, especially σ1 receptor (Fig. 2, bottom), which functions as a sensor for normal mitochondrial calcium (Ca^{2+}) operation (Weng et al., 2017) and σ1-ligands are thus discussed as protein-based pharmacological treatment to treat mitochondrial dysfunction in psychiatric and neurodegenerative conditions (Bolshakova et al., 2016).

Notably, agomelatine, a norepinephrine and dopamine disinhibitor (NDDI) and melatonergic MT1/2 agonist, was found to have a prominent positive effect on complex I in this meta-analysis (Figs. 1 and 2). Previous work showed that low-dose agomelatine increases complex I activity in prefrontal cortex, cerebellum, and striatum, while decreasing it in the posterior cortex, whereas high-dose agomelatine decreases complex I activity in all those brain regions (de Mello et al., 2015). Agomelatine is thought to protect against pathology-induced decreases in complex I (Gupta and Sharma, 2014; Kumar et al., 2015; Singh et al., 2015) by decreasing pathologically enhanced intracellular Ca^{2+} levels (Akpinar et al., 2014) and inhibiting the opening of mitochondrial permeability transition pores (Jia et al., 2018). This effect may be mediated by its agonist action at MT1 and MT2 receptors that have antioxidant activity and free radical scavenging, both actions are therapeutic for oxidative stress (Mahmood et al., 2016).

Ketamine, a NMDA receptor antagonist, used as rapidly acting antidepressant (Duman, 2018), was found to have a positive effect on complex IV (and to some extent complex I) (de Oliveira et al., 2011; Réus et al., 2015; Rezin et al., 2010; Venâncio et al., 2015) (Figs. 1 and 2). Previous work showed that ketamine increases complex IV but not complex I activity (Réus et al., 2015). In the short-term (1 h after treatment) it has been shown to increase complex IV activity in striatum and hippocampus but not in prefrontal cortex, whereas more delayed responses (after 6 h of treatment) were described only in striatum (de Oliveira et al., 2011). Ketamine also increases other enzymes such as peroxiredoxins that enhance cellular antioxidant capacity by combating reactive oxygen species, reducing protein damage and adjusting homeostatic redox, which supports the role of mitochondria as downstream effectors mediating its rapid antidepressant action

(Weckmann et al., 2017). Ketamine's effects on complex IV may be reflected in the strong positive effects of the ionotropic glutamatergic NMDA receptor (Fig. 2, bottom) that is co-regulated by the same transcription factors as COX (Wong-Riley, 2012) and thought to restore the neuroprotective glutamatergic system (Gough, 2012).

4.2. Antipsychotics

Antipsychotics show strong negative effects on complex I primarily accounted for by the typical antipsychotics, chlorpromazine, thiothixene, and haloperidol (Balijepalli et al., 2001, 1999; Barrientos et al., 1998; Burkhardt et al., 1993; Prince et al., 1998, 1997; Streck et al., 2007) (Figs. 1 and 2). Antagonism of dopaminergic, primarily D2, receptors by typical antipsychotics (Fig. 2, bottom) may lead to dopamine accumulation in mitochondria resulting in D2-induced inhibition of complex I (Ben-Shachar et al., 2004), which in turn has been associated with the induction of extrapyramidal side effects (EPS) (Burkhardt et al., 1993; Sykes et al., 2017). By contrast, haloperidol affects complex IV positively (Prince et al., 1997) as supported by our analysis (Fig. 1). These opposing haloperidol effects on complex I and IV are thought to result from either up-stream (D2-induced) inhibition of complex I in the ETC (Li et al., 2007) or reflect (D2-independent) enhanced functional neuronal activation due to the coupling between COX and neuronal activity (Wong-Riley, 2012). This in turn may be clinically reflected in the delayed therapeutic effects of neuroleptic agents (Prince et al., 1997).

By contrast, atypical antipsychotics were observed to have no significant effects besides an isolated increase in complex IV by risperidone (Balijepalli et al., 2001, 1999; Garabadu et al., 2015) (Fig. 1), which might be related to their lower affinity for D2 receptors relative to the serotonergic 5-HT$_{2A}$ (Corena-McLeod, 2015), adrenergic, muscarinic, and histaminic receptors (Mauri et al., 2014; Seeman, 2002), which also implies lower rates of extrapyramidal side effects.

Together, these results support a complex I participation in dopamine-induced mitochondrial dysfunction such as observed in postmortem brain samples from deceased schizophrenic patients (Ben-Shachar and Karry, 2008), whereas the reduction in COX activity observed in schizophrenia (Cavelier et al., 1995; Holper et al., 2018) is thought to be independent of antipsychotic treatment (Prince et al., 1997).

4.3. Anxiolytics

Evidence that anxiolytics have weak positive effects on complex IV, is not certain because of the small number of studies in this drug category. Only the benzodiazepine, diazepam, a GABA-A receptor positive allosteric modulator (PAM) (Fig. 2, top), enhanced complex IV (Fig. 1), suggesting that this GABA-A effect may not be the mechanism because all the other benzodiazepines do not have this effect on complex IV. The possibility of an effect of GABA-A receptors (Fig. 2, bottom) was thus not supported by our analysis but needs to be further evaluated when more subjects

have been studied because of the known neuroprotective effects of GABA-A agonists that may preserve COX activity by maintaining mitochondrial membrane potential, inhibiting downstream release of cytochrome c, and apoptotic signaling (Clarkson et al., 2007; Tyagi et al., 2009).

4.4. Mood stabilizers

Mood stabilizers show positive effects on both complex I and IV. Lithium, the most established mood stabilizer, increases complex I (Bachmann et al., 2009; Feier et al., 2013; Hroudová and Fisar, 2010; Kim et al., 2016; Lambert et al., 1999; Tan et al., 2012; Valvassori et al., 2010) (Figs. 1 and 2) by acting on intracellular Ca^{2+} signaling, inhibiting inositol monophosphatase (Kato, 2017), and modulating the neuroprotective ionotropic glutamatergic AMPA receptor (Gould et al., 2008), which, however, did not reach significance in our analysis (Fig. 2, bottom). These findings are consistent with human studies in postmortem brain of patients with bipolar depression that report lithium stimulating mitochondrial complex I (but not complex IV) at clinically relevant concentrations (de Sousa et al., 2015).

Antiepileptics, also used as mood stabilizers, such as gabapentin, enhance complex IV (Kumar et al., 2014, 2012) (Figs. 1 and 2), which may be related to their NMDA receptors antagonism (Chen et al., 2018) since it showed positive effects for other drugs as well (Fig. 2, bottom). The main action of AEDs is to increase GABA transmission, which did show effects (Fig. 2, bottom). Although, little is known about the impact of AEDs on mitochondria, our findings suggest that some AEDs like gabapentin and lamotrigine) have beneficial effects (or no effect) despite interfering with ETC-related membrane potential, mitochondrial biogenesis, morphology, dynamics, and survival (Finsterer and Scorza, 2017).

4.5. Stimulants

Stimulants such as amphetamine, methamphetamine, mazindol and methylphenidate, all dopamine reuptake inhibitors (DRIs), affect complex I negatively (Brown et al., 2005; Fagundes et al., 2010, 2007; Gonçalves et al., 2014; Killinger et al., 2014; Mishra et al., 2014; Thrash et al., 2010; Thrash-Williams et al., 2016, 2013) (Figs. 1 and 2) potentially related to their inhibition of DAT, NET and SERT transporters (Sitte and Freissmuth, 2015) (Fig. 2, bottom). Amphetamine enters and accumulates in mitochondria thereby dissipating the electrochemical gradient established by the ETC, inhibiting complex I and releasing cytochrome c, which in turn may induce the aforementioned interaction with complex IV and apoptosis (Lowinson et al., 2004).

4.6. Antidementia drugs

Antidementia drugs have no effects on complex I and it is not clear whether they affect complex IV (Figs. 1 and 2). Cholinesterase inhibitors (ChEIs), the most established antidementia drugs, inhibit ACh catabolism leading to its

accumulation, greater stimulation of nicotinic and muscarinic receptors, and disrupted neurotransmission that may explain some of their positive effects on learning, memory, and other cognitive functions in Alzheimer's (Čolović et al., 2013). Memantine, a NMDA antagonist, has a positive effect on complex IV (Kumar and Sharma, 2016; Réus et al., 2012; Singh et al., 2017) (Figs. 1 and 2) reflected in the strong positive NMDA receptor effect (Fig. 2, bottom) that is thought to restore unbalanced homeostasis in the glutamatergic system (Parsons et al., 2007). Positive effects on complex IV were also observed for latrepirdine (Singh et al., 2017) (Fig. 1); however, since its mechanism of action is not fully known its receptor affinity profile could not be assessed in the present analysis (Wishart et al., 2018), but may include neuroprotective effects by blocking neurotoxic Alzheimer beta-amyloid via modulation of NMDA receptors (Bachurin et al., 2006). Together, these findings suggest that the well-documented deficit in complex IV in Alzheimer's (Coskun et al., 2012; Giachin et al., 2016; Onyango et al., 2017), thought to be due to neuronal toxicity and hypometabolism induced by beta-amyloid accumulation in mitochondria (Cenini et al., 2016) can be addressed with antidementia drugs.

4.7.   Antiparkinsonian drugs

The most established antiparkinsonian drug, levodopa, an indirect dopamine agonist, was not found to affect complex I or IV (Abdin and Hamouda, 2008; Calabrese Vittorio et al., 2007; Dixit et al., 2013; Przedborski et al., 1993; Sharma et al., 2016). This is in contrast to previous findings stating that levodopa significantly increases complex I activity, while not changing complex IV activity (Calabrese Vittorio et al., 2007) or that levodopa does not alter complex I activity by itself, but attenuates the decrease in complex I activity induced by MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine), the prodrug to the neurotoxin MPP^+ (1-methyl-4-phenylpyridinium) which causes permanent symptoms of Parkinson's disease by destroying dopaminergic neurons in the substantia nigra (Dixit et al., 2013).

However, a weak positive effect on both complex I and IV was observed for selegiline, a selective irreversible MAO-B inhibitor in lower doses (Czerniczyniec et al., 2006) (Figs. 1 and 2). Selegiline is thought to be neuroprotective by suppressing Ca^{2+} efflux through mitochondrial permeability transition pores thereby inducing anti-apoptotic, pro-survival genes, though this is disputed (Wu et al., 2015). Selegiline could thus protect mitochondrial function when used to treat Parkinson's symptoms in combination with levodopa (Riederer et al., 2004), but also off-label as palliative treatment for Alzheimer's dementia (Birks and Flicker, 2003) and, as part of its antidepressant effects in major depressive disorder (Citrome et al., 2013).

4.8.   Summary of the meta-analyses

Summarizing the overall strength of mitochondrial changes caused by the seven drug categories indicates that antidepressants have the most heterogenous effects on both complex I and IV, which may be attributed to their broad

receptor profiles including affinity to adrenergic (α), histaminergic (H1-4), muscarinic (M1-5), opioid (OP1-3), serotonergic ($5\text{-}HT_{2A}$, $5\text{-}HT_{2C}$, $5\text{-}HT_{3A}$), and sigma (σ1) receptors. Typical versus atypical antipsychotics show strong negative effects on complex I versus weaker or no positive effects on complex IV, most likely associated with differential affinity for dopaminergic (D2), and serotonergic ($5\text{-}HT_{2A}$) receptors. Stimulants also exhibit strong negative effects on complex I, potentially related to their inhibition of DAT, NET, and SERT transporters. Because stimulants and typical antipsychotics share a negative effect on complex, it is unlikely to explain their opposite effects on positive symptoms of psychosis, worsened by stimulants and improved by antipsychotics. In contrast, positive effects on complex I and/or IV are observed for anxiolytics, mood stabilizers, antidementia, and antiparkinsonian drugs, potentially associated with GABAergic (GABA-A), glutamatergic (AMPA, NMDA), and nicotinic (nACh) receptor effects. Further research is required, to better understand the connection between the actions of therapeutic agents and mitochondrial complexes. This may contribute to the development of mitochondrial targeted treatments in psychiatric and neurogenerative disorders (Ben-Shachar and Ene, 2017).

4.9.   Methodological considerations

The present meta-analysis focused on rodent studies since no eligible studies were found in healthy human brain tissue. Doses and tissue levels of the cited drugs achieved in rodents are often much higher than those achieved in clinical treatment in humans. This is because the metabolism rate of drugs is much higher in rodents than in humans, and the higher doses are usually used to maximize effect but may create effects that are not clinically relevant. Such high doses may therefore have direct effects on mitochondrial electron transport, which may not be directly translatable to the effects expected at corresponding human doses. Further, we focused on drug effects at the neurotransmitter receptor and transporter level, but that is only one way drugs may indirectly alter mitochondrial activity. The observed considerable heterogeneity therefore needs to be considered indicating that not all effects can be explained at neurotransmitter receptors level. As an aside, the associations observed here are just "associations", they do not imply causality.

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L.H. collected the data, performed the analysis, and drafted the manuscript. B.BS. and J.J.M. provided helpful discussions and feedback to the manuscript. All authors agreed on the final version of the manuscript.

Conflict of interest

Acknowledgments

Supplementary material

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.euroneuro.2019.06.010.

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