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Published in:
Neuropharmacology

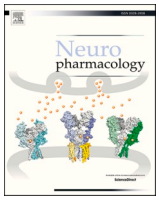
DOI:
10.1016/j.neuropharm.2023.109761

Neuropharmacology 242 (2024) 109761

Contents lists available at ScienceDirect

Neuropharmacology

journal homepage: www.elsevier.com/locate/neuropharm



Serotonergic and noradrenergic contributions to motor cortical and spinal motoneuronal excitability in humans

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ARTICLE INFO

Handling Editor: Bruno Frenguelli

Keywords:
Neuromodulation
Monoamine
Metabotropic
Corticospinal
Transcranial magnetic stimulation
Spinal reflex

ABSTRACT

Animal models indicate that motor behaviour is shaped by monoamine neuromodulators released diffusely throughout the brain and spinal cord. As an alternative to conducting a single study to explore the effects of neuromodulators on the human motor system, we have identified and collated human experiments investigating motor effects of well-characterised drugs that act on serotonergic and noradrenergic networks. In doing so, we present strong neuropharmacology evidence that human motor pathways are affected by neuromodulators across both healthy and clinical populations, insight that cannot be determined from a single reductionist experiment. We have focused our review on the effects that monoaminergic drugs have on muscle responses to non-invasive stimulation of the motor cortex and peripheral nerves, and other closely related tests of motoneuron excitability, and discuss how these measurement techniques elucidate the effects of neuromodulators at motor cortical and spinal motoneuronal levels. Although there is some heterogeneity in study methods, we find drugs acting to enhance extracellular concentrations of serotonin tend to reduce the excitability of the human motor cortex, and enhanced extracellular concentrations of noradrenaline increases motor cortical excitability by enhancing intracortical facilitation and reducing inhibition. Both monoamines tend to enhance the excitability of spinal motoneurons. Overall, this review details the importance of neuromodulators for the output of human motor pathways and suggests that commonly prescribed monoaminergic drugs target the motor system in addition to their typical psychiatric/neurological indications.

1. Introduction

Serotonin (5-HT) and noradrenaline (NA) exert several key neuromodulatory effects within motor circuits of the brain and spinal cord of animals (Heckman et al., 2008, 2009; Perrier and Cotel, 2015; Perrier et al., 2013; Vitrac and Benoit-Marand, 2017). The human motor cortex is innervated by ascending serotonergic and noradrenergic projections from the raphe nuclei and locus coeruleus respectively (Gaspar et al., 1989; Javoy-Agid et al., 1989; Raghanti et al., 2008), and *in vivo* animal studies indicate that 5-HT and NA increase the excitability of the motor cortex (Schiemann et al., 2015; Scullion et al., 2013). Motoneurons are the final output neurons for all motor behaviour and are also innervated by 5-HT and NA neurons descending from the brainstem (Alvarez et al., 1998; Rajaofetra et al., 1992). Based on animal studies, we also know that 5-HT and NA tend to increase the excitability of motoneurons and have been hypothesised to operate as gain controllers for muscle activation at a spinal level (Johnson and Heckman, 2014), thus enabling the scaling of motoneuron excitability to motor behaviour. In this light, computer simulations generated with data obtained from animal motoneuron experiments indicate that muscles would not even produce half of their maximal force in the absence of metabotropic inputs, even when ionotropic input is maximal (Heckman et al., 2008).

Most of the work concerning neuromodulation (note: this is a physiological process and is not to be confused with 'neuromodulatory' technologies), and its effects on motor circuits in the brain and spinal cord, have involved slice preparation experiments. However, mechanisms derived from *in vitro* work do not always explain neurophysiological processes within the intact human nervous system, whereby the inputs to and voltage properties of individual human neurons cannot be directly measured or controlled *in vivo*. To better determine whether results from reductionist preparation experiments align with human motor behaviour, several 5-HT and NA active drugs have been used off-

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https://doi.org/10.1016/j.neuropharm.2023.109761
Received 4 July 2023; Received in revised form 5 October 2023; Accepted 11 October 2023
Available online 12 October 2023

label as a tool to target the activity of neuromodulators or their associated receptors, and post-drug changes in motor behaviour subsequently studied and compared to a placebo or drug free condition. Alternatively, many clinical studies use monoaminergic drugs as an intervention for movement disorders and these studies are an untapped resource for understanding how neuromodulators affect human motor activity. In both situations, monoaminergic drugs either mimic or 'knockout' the typical physiological effects exhibited by 5-HT and NA in the nervous system, thus enabling causative links to be derived between monoamines and movement in intact human volunteers. When neurostimulation and other closely related techniques are paired with well-characterised drug interventions, better links can be made between human, animal, and *in vitro* mechanisms concerning neuromodulation.

There has not yet been an effort to amalgamate human studies involving both: i) the administration of 5-HT or NA drugs and ii) lab-based measures of corticospinal-motoneuronal excitability. In this review we gather and report human studies that have examined the effects of serotonergic and noradrenergic medications on muscle responses to magnetic or electrical stimulation of the motor cortex and peripheral nerves, and other closely related tests of motoneuron excitability (reflex responses to vibration or stretch, and electromyography-derived estimates of motoneuronal persistent inward current amplitude, i.e., PIC amplitude). The serotonergic and noradrenergic medications used in these drug experiments are described in Table 1, and the results of experiments summarised in Tables 2–4 and Appendix 1. Using what we know about the physiology of the abovementioned lab-based electrophysiology measures, and a synthesis of the results from the studies we identified, we speculate on how neuromodulators shape the output of the human brain and spinal circuits that activate muscle.

2. The serotonin system

2.1. Serotonergic effects on resting muscle responses to motor cortical stimulation

Throughout this review, drug effects on lab-based measures of corticospinal-motoneuronal excitability are summarised in tables. Table 2 indicates that 5-HT drugs have complex effects on the excitability of the motor cortex and corticospinal pathway in awake human subjects (Acler et al., 2009; Batsikadze et al., 2013; Bonin Pinto et al., 2019; Busan et al., 2009; Eichhammer et al., 2003; Gerdelat-Mas et al., 2005; Henderson et al., 2022; Ilic et al., 2002; Jeng et al., 2020; Khedr et al., 2020; Kuo et al., 2016; Lagas et al., 2016; McDonnell et al., 2018; Melo et al., 2021; Minelli et al., 2010; Nitsche et al., 2009; Pleger et al., 2004; Robol et al., 2004; Thorstensen et al., 2020, 2021; Werhahn et al., 1998). Motor cortical transcranial magnetic stimulation (TMS) activates the axons of corticospinal cells directly or via the activation of intracortical neurons that directly synapse onto these cells. Consequently, TMS of the motor cortex generates several descending volleys that arrive at spinal motoneurons, generating a compound muscle action potential that can be recorded with surface electromyography (EMG) at the muscle as a motor evoked potential (MEP). The physiology of TMS has been reviewed in detail elsewhere (Hallett, 2000; Terao and Ugawa, 2002; Wasserman et al., 2008), however it is important to note that, the MEP provides an index of excitability for the whole motor pathway from cortex to muscle and is thus influenced by excitability changes at both the motor cortex and motoneurons (McNeil et al., 2013).

In three studies (Gerdelat-Mas et al., 2005; Ilic et al., 2002; Khedr et al., 2020), single dose administration of the selective serotonin reuptake inhibitors (SSRIs) paroxetine or sertraline increased the size of MEPs obtained at rest (i.e., when there is no descending drive to the muscle), denoting an increase in corticospinal-motoneuronal excitability. Yet longer-term administration of the SSRI paroxetine was also

Table 1
The actions of serotonin and noradrenaline active drugs used in included studies.

	Drug class	Drug/s included in this review	Mechanism of action	5-HT and NA effect/s
Serotonin (5-HT)	SSRI	Citalopram, Sertraline, Fluoxetine, Paroxetine, Escitalopram, Fluvoxamine	Reduce pre-synaptic reuptake of 5-HT	↑ in extracellular 5-HT
	5-HT_2 antagonist	Cyproheptadine	Reduce 5-HT_2 receptor activation	↓ 5-HT_2 receptor activation
	5-HT_{1A} agonist	Buspirone	Activation of 5-HT_{1A} receptor	↑ 5-HT_{1A} receptor activation
	5-$HT_{1B/1D}$ agonist	Zolmitriptan	Activation of 5-$HT_{1B/1D}$ receptor	↑ 5-$HT_{1B/1D}$ receptor activation
Noradrenaline (NA)	Psychostimulant	Amphetamine, Amphetaminil, Methylamphetamine	NA & DA release Monoamine oxidase inhibitor	↑ in extracellular NA & DA
	NRI	Reboxetine, Atomoxetine	Reduce pre-synaptic reuptake of NA	↑ in extracellular NA
	NDRI	Methylphenidate	Reduce pre-synaptic reuptake of NA & DA	↑ in extracellular NA & DA
	α_2 antagonist	Yohimbine	Reduce α_2 receptor activation	↓ α_2 receptor activation ↑ in extracellular NA
	α_2 agonist	Guanfacine, Clonidine	Activation of α_2 receptor	↑ α_2 receptor activation ↓ in extracellular NA
	α_1 antagonist β antagonist (non-selective)	Prazosin, Thymoxamine, Indoramin Propranolol	Reduce α_1 receptor activation Reduce β_1 and β_2 receptor activation	↓ α_1 receptor activation ↓ β_1 and β_2 receptor activation
Combined 5-HT and NA effects	SNRI	Venlafaxine	Reduce pre-synaptic reuptake of 5-HT & NA	↑ in extracellular 5-HT & NA
	α_2/5-HT_2 antagonist	Mirtazapine	Reduce α_2 receptor activation Reduce 5-HT_2 receptor activation	↓ α_2 receptor activation ↑ in extracellular NA ↓ 5-HT_2 receptor activation
	α_1/5-HT_2 antagonist	Chlorpromazine	Reduce α_1 receptor activation Reduce 5-HT_2 receptor activation	↓ α_1 receptor activation ↓ 5-HT_2 receptor activation

5-HT = 5-hydroxytryptamine/serotonin, DA = dopamine, NA = noradrenaline, NDRI = noradrenaline dopamine reuptake inhibitor, NRI = noradrenaline reuptake inhibitor, SNRI = serotonin noradrenaline reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor.

Table 2
Results of studies assessing effects of serotonin drugs on motor cortical and motoneuronal excitability.

Corticospinal excitability with TMS		RMT	AMT	Resting MEP	Active MEP	ICF	SICI	LICI	Silent period
Population	**Drug class**								
Healthy	SSRI	○ ○ ○ ○ ○ ○ ▲	○ ○ ○	○ ○ ○ ○ ○ ○ ▲ ▲	○ ○	▼ ▼ ○ ○	○ ○ ▲ ▲		○ ▲ ▲ ▲
	SSRI (chronic)	○ ○	○	▼ ○		▲	○		○
	5-HT_2 antagonist		○		▼				▲
	5-$HT_{1B/1D}$ agonist	○		○	○	○	▼		○
Depression	SSRI	▲		○ ▲	▲	▼	▲		○
	SSRI (chronic)					○	○	▼	
Stroke	SSRI (chronic)	Affected ○ Unaffected ▲		Affected ○ Unaffected ○		Unaffected ▲	Affected ○ Unaffected ▲		
Stuttering	SSRI (chronic)	○	○						▼
Motoneuron excitability		**CMEP**	**H-reflex**	**Stretch reflex**	**Vibratory reflex**	**Cutaneous reflex**	**F-waves**	**Estimates of PICs**	**Silent period**
Population	**Drug class**								
Healthy	SSRI				▲		○ ○ ○ ▼*	▲	▲
	SSRI (chronic)						○		
	5-HT_2 antagonist	○					▼	▼	
	5-$HT_{1B/1D}$ agonist		▼						
	5-HT_{1A} agonist	▼					▼		
Depression	SSRI						○		
	SSRI (chronic)						○		
Stroke	SSRI			Affected ▲					
	5-HT_2 antagonist (chronic)			Affected ○					
SCI	SSRI			▲		▲			
	5-HT_2 antagonist			▼		▼ ▼		▼	
	5-$HT_{1B/1D}$ agonist		▼			▼			

All studies involved single dose administration of a drug unless indicated as chronic (administration over weeks or months). ○ = no change in outcome, ▼ = decrease, ▲ = increase. For stroke studies, effects have been dichotomised for the affected and unaffected hemispheres (TMS studies), or affected and unaffected limbs (motoneuron excitability studies). 5-HT = 5-hydroxytryptamine/serotonin, AMT = active motor threshold, CMEP = cervicomedullary motor evoked potential, ICF = intracortical facilitation, LICI = long-interval intracortical inhibition, MEP = motor evoked potential, PICs = persistent inward currents, RMT = resting motor threshold, SCI = spinal cord injury, SICI = short-interval intracortical inhibition, SSRI = selective serotonin reuptake inhibitor, TMS = transcranial magnetic stimulation. For references, see main text and Appendix 1. *For F-waves, one study found a SSRI-mediated decrease only for fatigued muscle, but all other studies report drug effects in an unfatigued state.

shown to decrease the resting MEP (Gerdelat-Mas et al., 2005), indicating that the number of SSRI administrations influences the direction of MEP size changes (i.e., whether a MEP gets larger or smaller in response to a drug intervention). Compared to single dose administration of an SSRI, the repeated administration over several weeks causes a de-sensitisation of 5-HT responsive inhibitory 5-HT_1 auto receptors and more 5-HT release (Stahl, 1998), potentially explaining the divergence of resting MEP findings between single and repeated doses of SSRI.

Corticospinal-motoneuronal excitability can also be assessed by TMS threshold measures, i.e., the minimum motor cortical stimulation intensity needed to evoke a MEP, whereby decreases in threshold denote increased excitability. Yet, the stimulation intensity needed to reach resting motor threshold (RMT) is not consistently affected by serotonergic drugs (Busan et al., 2009; Eichhammer et al., 2003; Gerdelat-Mas et al., 2005; Ilic et al., 2002; Lagas et al., 2016; McDonnell et al., 2018; Pleger et al., 2004; Werhahn et al., 1998), except for a small minority of studies whereby the SSRI citalopram increases threshold (Acler et al., 2009; Minelli et al., 2010; Robol et al., 2004). RMT is typically defined as the intensity needed to elicit a MEP of 50 μV peak-peak amplitude in at least 50% of stimulations (Groppa et al., 2012; Rossini et al., 2015). Stimulation intensities at RMT activate the cortico-cortical and corticospinal projections most easily excited by the magnetic pulse, and most likely lower-threshold spinal motoneurons if descending volley/s are evoked. Hence, the absence of clear and consistent 5-HT drug effects on RMT indicates that serotonergic projections to the motor cortex may not affect lower threshold TMS-recruited inputs to motoneurons, and/or the excitability of smaller motoneurons usually activated by lower levels of excitatory synaptic input. Findings may also indicate that lower-intensity TMS assesses excitability components of interneurons and/or corticospinal cells that are not strongly mediated by neuromodulators (e.g., axonal excitability or the magnitude of pre-synaptic glutamate release). Likewise, compared to suprathreshold stimulation (i.e., stimulation 120% RMT and greater) that recruits a larger sample of corticospinal neurons and/or motoneurons into the resting MEP, the excitability of a smaller portion of the corticospinal-motoneuronal pathway is assessed at threshold level stimulation. To this end, TMS may not be sensitive enough to pick up serotonergic effects on excitability with lower-intensity stimulation.

2.2. *Intracortical facilitation and inhibition are modulated by 5-HT drugs*

When conditioned by a preceding stimulation to the same site of the motor cortex, the amplitude of the resting MEP provides an index of intracortical inhibitory or facilitatory strength (Hallett, 2000; Kujirai et al., 1993; Rossini et al., 2015; Terao and Ugawa, 2002; Wasserman et al., 2008; Ziemann et al., 1996). At very short interstimulus intervals (typically 2–3 ms), a subthreshold conditioning stimulus reduces the amplitude of a proceeding suprathreshold stimulation evoked test MEP to reflect short interval intracortical inhibition (SICI). At an interstimulus interval of ~10 ms, the effect of a subthreshold conditioning stimulation increases the size of the MEP, and this is deemed intracortical facilitation (ICF). Long interval intracortical inhibition (LICI) is observed when two suprathreshold stimulations are separated by 100 ms. Regarding paired pulse TMS, several studies indicate that single dose administration of SSRIs such as citalopram, paroxetine or sertraline decrease measures of facilitation and increase measures of inhibition

Table 3
Results of studies assessing effects of noradrenaline drugs on motor cortical and motoneuronal excitability.

Corticospinal excitability with TMS		RMT	AMT	Resting MEP	Active MEP	ICF	SICI	LICI	Silent period
Population	**Drug class**								
Healthy	Amphetamine/ Amphetamine prodrug	○ ○ ○ ○ ○		▼ ○ ○ ○ ○ ▲		○ ▲	○		
	NRI	▼ ○ ○ ○ ○ ○ ○	○ ○	○ ○ ▲ ▲ ▲ ▲	○ ○ ▲	▲ ▲ ▲ ▲ ▲ ▲	▼ ▼ ▼ ○ ○		○ ○ ○
	NRI (chronic)	○ ○	○	▲		○ ▲	○ ▼		
	NDRI	○ ○ ○ ○ ○ ○ ○	○ ○ ○ ○	○ ○ ○ ○ ▲	○	○ ▲ ▲ ▲	▼ ▼ ○ ○ ▲		○ ○ ○
	NDRI (chronic)	○		▲		○ ▲	○ ▼	▼ ○	
	α_2 antagonist	○		▲		▲	○		
	α_2 agonist	○	○	▼		▼	▲		○
	α_1 antagonist	○ ○	○	○ ○ ▲		○	○		○
	β antagonist	○	○	○ ○		○	○		○
ADHD with Tourette Syndrome	NRI	○	○	○		▲	○ ▲		
	NRI (chronic)	○	○	○		○	○		
	NDRI						▲		
ADHD	NRI						▼		
	NDRI	○ ○	○			○	▼ ▲		○ ○
	NDRI (chronic)	○ ○ ○ ○	○	○ ○ ○		○ ▲	▲ ▲	▲	○
Stroke	NRI			Affected ○ Unaffected ○					
Motoneuron excitability		**CMEP**	**H-reflex**	**Stretch reflex**	**Vibratory reflex**	**Cutaneous reflex**	**F-waves**	**Estimates of PICs**	**Silent period**
Population	**Drug class**								
Healthy	Amphetamine/ Methylamphetamine		○ ▲	▲ ▲			○	▲	
	NRI		○ ○ ▲				○		
	NDRI						○		○
	α_2 antagonist						○		
	α_2 agonist			▼			○		○
	α_1 antagonist		○	▼ ▼					
	β antagonist		○	○ ▲					
Brain/spinal cord lesions (otherwise undefined)	α_1 antagonist		▼	▼ ▼	▼	○			
	β antagonist		○	○					

All studies involved single dose administration of a drug unless indicated as chronic (administration over weeks or months). ○ = no change in outcome, ▼ = decrease, ▲ = increase. For the single stroke study, effects have been dichotomised for the affected and unaffected hemispheres. ADHD = attention-deficit/hyperactivity disorder, AMT = active motor threshold, CMEP = cervicomedullary motor evoked potential, ICF = intracortical facilitation, LICI = long-interval intracortical inhibition, MEP = motor evoked potential, NDRI = noradrenaline dopamine reuptake inhibitor, NRI = noradrenaline reuptake inhibitor, PICs = persistent inward currents, RMT = resting motor threshold, SICI = short-interval intracortical inhibition, TMS = transcranial magnetic stimulation. For references, see main text and Appendix 1.

(Eichhammer et al., 2003; Gerdelat-Mas et al., 2005; Ilic et al., 2002; Minelli et al., 2010; Robol et al., 2004). Although it is tempting to conclude that 5-HT has a net effect of reducing intracortical excitability, separate intracortical circuits likely contribute to the conditioning of a MEP for ICI and ICF responses and these circuits do not necessarily overlap (Ziemann et al., 1996). Importantly, the preceding short interval conditioning pulse that is used to reduce the size of the MEP preferentially activates low threshold inhibitory cells that generate inhibitory postsynaptic potentials (IPSPs) in excitatory cortical interneurons and/or corticospinal cells (Paulus et al., 2008; Ziemann et al., 2015). Hence, the enhanced availability of 5-HT with SSRI administration perhaps augments the magnitude and/or efficacy of inhibitory intracortical neurotransmission. Regardless of the exact mechanism underlying SICI, activation of the 5-$HT_{1B/1D}$ receptor with zolmitriptan reduces SICI (Werhahn et al., 1998), indicating that the 5-HT_1 receptor may be involved. For ICF, enhanced 5-HT availability might decrease the excitability of an intracortical facilitatory circuit that is also activated by a subthreshold conditioning pulse to the motor cortex, so that the suprathreshold test pulse recruits less corticospinal neurons that are usually facilitated by these excitatory intracortical inputs.

In contrast to single dose SSRI administration, longer-term use of SSRIs (e.g., paroxetine and escitalopram) increase ICF in healthy participants (Gerdelat-Mas et al., 2005) and decrease LICI in individuals with depression (Jeng et al., 2020), indicating that drug-induced increases or decreases in conditioned MEPs depend on the number of SSRI doses. In the unaffected hemisphere of individuals with stroke, chronic administration of the SSRI fluoxetine increases ICF (Bonin Pinto et al., 2019), but both decreases (with chronic fluoxetine) and increases (chronic citalopram) in SICI have been observed in separate studies (Acler et al., 2009; Bonin Pinto et al., 2019).

2.3. 5-HT drugs affect muscle responses to motor cortical stimulation during voluntary contraction

Motor cortical TMS can be applied when the target muscle is voluntarily activated (i.e., to obtain an 'active' MEP, usually during brief isometric contractions). MEPs obtained during muscle contraction are larger than those obtained in resting muscle, as there is ongoing voluntary activation of the motor cortex and motoneurons (McNeil et al., 2013). Compared to rest, more motoneurons are in the subliminal fringe and closer to their firing thresholds. This means that TMS is better able to recruit more motoneurons into the MEP and assess the excitability of a larger sample of efferent projections to muscle. When the muscle is pre-activated by voluntary activity, whereby voluntary contractions probably cause some natural release of 5-HT to motoneurons (Jacobs et al., 2002; Veasey et al., 1995), the SSRI paroxetine does not appear to affect the size of active MEPs in healthy participants (Henderson et al., 2022; Thorstensen et al., 2020). Yet, an isolated study investigating single dose administration of the SSRI sertraline found an increase in active MEP size in individuals with depression (Khedr et al.,

Table 4
Results of studies assessing effects of drugs with combined serotonin and noradrenaline properties on motor cortical and motoneuronal excitability.

Corticospinal excitability with TMS		RMT	AMT	Resting MEP	Active MEP	ICF	SICI	LICI	Silent period
Population	**Drug class**								
Healthy	SNRI	○		○					
	SNRI (chronic)	○		○					
	α_2/5-HT_2 antagonist	○	○	○	○	○	○		▲
Depression	SNRI (chronic)					○	○		○
Depression with epilepsy	α_2/5-HT_2 antagonist	○	▼	○	○	○	○		○
	α_2/5-HT_2 antagonist (chronic)	○	○	○	○	○	○		○
Stroke	SSRI or SNRI (chronic)	Affected ○ Unaffected ○		Affected ○ Unaffected ○					
Motoneuron excitability		**CMEP**	**H-reflex**	**Stretch reflex**	**Vibratory reflex**	**Cutaneous reflex**	**F-waves**	**Estimates of PICs**	**Silent period**
Population	**Drug class**								
Healthy	α_1/5-HT_2 antagonist		▼ ○ ○	▼ ▼				▼	
SCI	α_1/5-HT_2 antagonist					○			
Brain injury/SCI	α_1/5-HT_2 antagonist			▼					
Schizophrenia	α_1/5-HT_2 antagonist		○						

All studies involved single dose administration of a drug unless indicated as chronic (administration over weeks or months). ○ = no change in outcome, ▼ = decrease, ▲ = increase. For the single stroke study, effects have been dichotomised for the affected and unaffected hemispheres. AMT = active motor threshold, CMEP = cervicomedullary motor evoked potential, ICF = intracortical facilitation, LICI = long-interval intracortical inhibition, MEP = motor evoked potential, PICs = persistent inward currents, RMT = resting motor threshold, SCI = spinal cord injury, SICI = short-interval intracortical inhibition, SNRI = serotonin noradrenaline reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor, TMS = transcranial magnetic stimulation. For references, see main text and Appendix 1.

2020). Although speculative, the active motor cortex and/or motoneuron pools in individuals with depression may be more sensitive to 5-HT effects from the SSRI, compared to neurotypical individuals. Also of note, antagonism of the 5-HT_2 receptor with cyproheptadine decreases the size of MEPs obtained during muscle contractions in healthy participants (Thorstensen et al., 2021). The active motor threshold (AMT), typically the stimulation intensity required to elicit a 200 μV peak-to-peak MEP during weak isometric contraction (in at least 50% of stimulations) (Groppa et al., 2012; Rossini et al., 2015), is not affected by 5-HT drugs (Busan et al., 2009; Eichhammer et al., 2003; Gerdelat-Mas et al., 2005; Ilic et al., 2002; Thorstensen et al., 2021).

Motor cortical TMS can also be used to elucidate corticospinal-motoneuronal inhibitory mechanisms during muscle activity. After the active TMS-evoked MEP there is a transient interruption to the voluntary activation of motoneurons, which is measured as a silent period in the ongoing EMG signal (Hupfeld et al., 2020; Skarabot et al., 2019). A longer duration silent period denotes more inhibitory activity within the motor cortex and/or at motoneurons, whereby the latter part of the silent period is likely attributed to long-lasting intracortical inhibition mediated by γ-aminobutyric acid (GABA) receptors (Paulus et al., 2008; Ziemann et al., 2015). Although paired pulse measures of inhibition likely reflect a different inhibitory mechanism/s than those that cause the TMS-induced silent period, 5-HT mediated increases in paired pulse measures of inhibition are further corroborated by silent period findings across several studies, whereby single dose administration of the SSRI paroxetine or citalopram lengthens the TMS-induced silent period in healthy subjects (Henderson et al., 2022; Robol et al., 2004; Thorstensen et al., 2020). In this regard, enhanced 5-HT availability from the SSRIs could have caused a longer-lasting TMS-induced inhibition of corticospinal cells during voluntary contraction. A longer-lasting inhibition of motor cortical projections to motoneurons will cause a longer-lasting dis-facilitation of the motoneurons voluntarily recruited into contraction, resulting in the SSRI mediated lengthening of the TMS-induced silent period. Interestingly, antagonism of the 5-HT_2 receptor with cyproheptadine also increases silent period duration (Thorstensen et al., 2021). In an isolated study (Busan et al., 2009), repeated-dose administration of the SSRI paroxetine shortens the TMS-induced silent period, which provides further evidence that the direction of SSRI effects on TMS-induced muscle responses depend on the number of SSRI exposures. Consistent with TMS-induced silent period findings, the peripherally induced EMG silent period in a hand muscle (evoked through cutaneous electrical stimuli to the finger) is also lengthened by the single dose of the SSRI escitalopram (Pujia et al., 2014).

2.4. A complex role for 5-HT in the excitability of motoneurons to corticospinal stimulation and antidromic activation

With TMS of the motor cortex, all evoked volleys that descend via corticospinal axons must pass through synapses with motoneurons and spinal interneurons before arriving at muscle fibres to be recorded as a MEP. Hence, the size of TMS-evoked muscle responses is heavily influenced by the excitability of sensorimotor circuits in the spinal cord. Considering this, tests of motoneuron excitability help elucidate whether changes to cortically evoked responses are due to supraspinal or spinal changes (McNeil et al., 2013). Indeed, tests of motoneuron excitability indicate that 5-HT drugs have strong effects in the human spinal cord (D'Amico et al., 2017; D'Amico et al., 2013a; D'Amico et al., 2013b; Gerdelat-Mas et al., 2005; Goodlich et al., 2023; Gourab et al., 2015; Ilic et al., 2002; Kamper et al., 2022; Kavanagh et al., 2019; Minelli et al., 2010; Murray et al., 2010; Pujia et al., 2014; Robol et al., 2004; Sattler et al., 2000; Thorstensen et al., 2022; Wei et al., 2014) (see Table 2).

Electrical or magnetic stimulation at the cervicomedullary junction, which evokes cervicomedullary motor evoked potentials (CMEPs) in upper-limb muscles, is a valid spinal level control for MEPs in upper-limb muscles, as it activates many of the same inputs to motoneurons as TMS of the motor cortex (Taylor, 2006; Taylor and Gandevia, 2004). CMEPs have a strong monosynaptic component for proximal upper-limb muscles such as the biceps brachii (Petersen et al., 2002). We only identified two studies which assessed the effects of 5-HT drugs on CMEPs. Importantly, for the resting biceps brachii, 5-HT_2 receptor antagonism with cyproheptadine does not affect CMEPs (Thorstensen et al., 2022), but 5-HT_{1A} receptor agonism with buspirone reduces their size in healthy individuals (D'Amico et al., 2017). There are several key

explanations that may explain these results. Regarding the somato-dendritic Gq coupled 5-HT_2 receptor, animal (Harvey et al., 2006a, 2006b; Murray et al., 2011a; Perrier and Delgado-Lezama, 2005; Perrier and Hounsgaard, 2003) and human studies (D'Amico et al., 2013b; Goodlich et al., 2023) indicate that this receptor increases motoneuron excitability by facilitating dendritic voltage-gated PICs, thus greatly increasing the input-output gain of motoneurons to descending or sensory ionotropic inputs, and causing the prolonged discharge of motoneurons. Yet in a resting motoneuron pool, the size of a CMEP is unlikely to reflect the contribution of dendritic PICs to motoneuron excitability (especially the component of the total PIC mediated by slowly activating Ca^{2+} channels). This is because cervicomedullary stimulation probably only causes a brief excitatory postsynaptic potential (EPSP) in motoneurons but sustained excitatory input (lasting at least half a second in duration) is needed to cause repetitive firing of motoneurons and PIC activation (Li et al., 2004). This contrasts with the Gi/Go coupled 5-HT_{1A} receptor which is located at the axon initial segment (i.e., the site responsible for spike initiation) and shown to reduce motoneuron excitability in turtle preparations (Cotel et al., 2013; Perrier et al., 2017). In this regard, it seems most likely that agonism of 5-HT_{1A} receptors reduces the size of CMEPs because less motoneurons can transmit the single spike past the initial segment and towards the muscle.

Considering the extra-synaptic location of the 5-HT_{1A} receptor, it is not entirely clear if or when the 5-HT_{1A} receptor is activated during human motor behaviour. 5-HT has a remarkable ability to increase the excitability of turtle, rat, and cat motoneurons (Perrier and Cotel, 2015; Perrier et al., 2013), and the initial segment 5-HT_{1A} receptor is perhaps only activated when the concentration of 5-HT in the synapse is sufficiently high, and 5-HT diffuses away from the synapse (Cotel et al., 2013; Perrier et al., 2017). There were no studies combining SSRI administration and cervicomedullary stimulation to investigate this possibility.

The supramaximal electrical stimulation of a peripheral motor nerve evokes antidromic spikes, which cause the recurrent orthodromic discharge of a small number of higher-threshold motoneurons, and these discharges are recorded with EMG in the resting muscle as F-waves (Fisher, 1992; McNeil et al., 2013; Mesrati and Vecchierini, 2004). Recent investigations provide evidence that the F-wave is generated through synaptic connections between motoneurons via recurrent motor axon collaterals (Özyurt et al., 2023), but the classical interpretation of F-waves are that they are the consequence of a "rebound" discharge of the same motoneurons activated antidromically. Whatever the mechanism generating F-waves, the SSRIs paroxetine, sertraline, citalopram and fluvoxamine do not affect F-wave amplitude or persistence (Gerdelat-Mas et al., 2005; Ilic et al., 2002; Kavanagh et al., 2019; Minelli et al., 2010; Robol et al., 2004; Sattler et al., 2000), indicating that enhanced synaptic 5-HT alone does not affect the recurrent discharge of motoneurons to antidromic activation. Yet, when F-waves are obtained directly after fatiguing muscle contractions in the presence of SSRI administration, which in combination likely cause large extracellular concentrations of 5-HT to be present in the spinal cord, they are smaller compared to placebo (Kavanagh et al., 2019). This finding is consistent with the 5-HT 'spill over' hypothesis of central fatigue demonstrated in turtle preparations (Cotel et al., 2013; Perrier et al., 2017). In turtle preparations, prolonged stimulation of serotonergic projections to motoneurons results in a high concentration of synaptic 5-HT and causes 5-HT to diffuse away from the synapse and activate extra synaptic inhibitory 5-HT_{1A} receptors (that act to reduce motoneuron spiking). In humans, increases in extracellular 5-HT levels from the SSRI likely causes more spill over and greater 5-HT_{1A} receptor activation to decrease the likelihood of motoneurons generating a recurrent discharge and subsequent F-wave. In support of a 5-HT_{1A} receptor locus for SSRI-mediated reductions in F-waves of fatigued muscle, the pharmacological activation of this receptor with the agonist buspirone also reduces F-waves (D'Amico et al., 2017), but a reduction in F-waves has also been reported with 5-HT_2 antagonism after cyproheptadine administration (Thorstensen et al., 2022).

2.5. The excitability of motoneurons to sensory afferent input is modulated by 5-HT drugs

Motoneurons can be reflexively recruited by the electrical or mechanical activation of sensory inputs in the periphery, and muscle responses to sensory afferent activation provide an index of excitability for sensorimotor circuits at the level of the spinal cord. For example, the electrical stimulation of Ia afferent axons provides a synchronous recruitment of motoneurons and elicits EMG recorded H-reflexes, the size of which may provide an index of motoneuron excitability to sensory input (Misiaszek, 2003; Theodosiadou et al., 2023; Zehr, 2002). Activation of the 5-$HT_{1B/1D}$ receptor with the agonist zolmitriptan reduces the size of H-reflexes in both healthy participants and in individuals with spinal cord injury (D'Amico et al., 2013a). Yet, the electrical properties of Ia afferent fibres can modify sensory transmission to motoneurons (Rudomin and Schmidt, 1999; Stein, 1995), and a reduction in H-reflexes can be a consequence of pre-synaptic and not motoneuron excitability changes, or a combination of both pre- and post-synaptic changes. In this light, in addition to motoneurons that express 5-HT_1 receptors (Perrier et al., 2013), sensory afferents also express 5-HT_1 receptors that when activated, inhibit the output of segmental inputs to motoneurons (Murray et al., 2011b). The 5-$HT_{1B/1D}$ receptor could reduce the H-reflex through reductions in sensory transmission, whereby activation of this inhibitory receptor reduces the EPSP generated by Ia afferent and/or excitatory interneurons. Consequently, motoneurons are less likely to be recruited into the H-reflex, even though post-synaptic excitability is presumably unaffected by a 5-$HT_{1B/1D}$ agonist.

Unlike the highly synchronous afferent volley from the electrical stimulation of sensory fibres, which causes a brief EPSP in motoneurons, stretch reflexes like the tendon tap/jerk cause a more dispersed volley comprising multiple discharges and is longer in duration (Burke et al., 1983). The SSRI escitalopram increases the amplitude of stretch reflexes, and 5-HT_2 receptor antagonism with cyproheptadine decreases stretch reflexes in individuals with chronic spinal cord injury (Wei et al., 2014). Moreover, trains of electrical stimuli can be applied to the skin at the foot to evoke cutaneous reflexes in lower-limb muscles, and are enhanced by single dose SSRI administration but reduced by 5-HT_2 antagonism and 5-$HT_{1B/1D}$ agonism in chronic spinal cord injured individuals (D'Amico et al., 2013a; D'Amico et al., 2013b; Murray et al., 2010). It should be noted that even weak excitatory input can cause a long-lasting involuntary firing of motoneurons in chronic spinal cord injured subjects (D'Amico et al., 2014). This motoneuronal hyperexcitability is partly due to plastic changes in monoaminergic receptors, such as the 5-HT_2 receptor, which becomes constitutively active, facilitates PICs and augments muscle spasticity (D'Amico et al., 2013b; Murray et al., 2010). Hence, individuals with chronic spinal cord injury are likely very sensitive to 5-HT drug interventions, and it is unlikely that a similar magnitude of 5-HT drug mediated changes in reflex amplitudes would be observed in intact human participants with a preserved descending control of motoneurons. In individuals with stroke, single dose administration of the SSRI escitalopram increases paretic limb stretch reflexes (Gourab et al., 2015), perhaps implicating 5-HT in the pathophysiology of post-stroke spasticity. Vibration reflexes also cause the reflexive recruitment of motoneurons, whereby motoneurons can be activated repetitively via monosynaptic input from peripheral afferents when a muscle or tendon is subjected to sustained vibration (Monjo and Shemmell, 2020). Although assessed in resting muscle, and hence under conditions with weak serotonergic drive to the spinal cord (Jacobs et al., 2002; Veasey et al., 1995), the SSRI escitalopram enhances the magnitude of vibratory reflexes in healthy subjects (Wei et al., 2014), indicating a net facilitatory effect of increased extracellular 5-HT on resting motoneurons. Vibration will provide a sustained ionotropic input to

motoneurons, which allows the activation of slowly activating PICs, so 5-HT drug effects on muscle responses to vibration may approximate 5-HT effects on PICs for human motoneurons.

3. The noradrenaline system

3.1. Noradrenaline increases the size of muscle responses to motor cortical stimulation

Table 3 presents the effects of noradrenaline drugs on corticospinal-motoneuronal excitability. Compared to the number of TMS experiments investigating 5-HT drugs, there were many more examining NA active drugs (Berger et al., 2018; Boroojerdi et al., 2001; Buchmann et al., 2006, 2007, 2010; Butefisch et al., 2002; Foster et al., 2006; Gilbert et al., 2006a, 2006b, 2007; Herwig et al., 2002; Hoeppner et al., 2008; Ilic et al., 2003; Kesar et al., 2017; Kirschner et al., 2003; Klass et al., 2012, 2016, 2018; Korchounov et al., 2003; Korchounov and Ziemann, 2011; Kratz et al., 2009; Kuo et al., 2017a, 2017b; Lange et al., 2007; Meintzschel and Ziemann, 2006; Moll et al., 2000, 2003; Nitsche et al., 2004; Ozdag et al., 2010; Plewnia et al., 2001, 2002, 2004; Sawaki et al., 2002, 2003; Schneider et al., 2011; Sczesny-Kaiser et al., 2014; Ziemann et al., 2002; Zittel et al., 2007). Hence, there has been considerable interest regarding noradrenergic transmission within human motor pathways, and how NA drugs affect muscle responses to TMS of the motor cortex.

Across the NA drug studies that we identified; it was consistently demonstrated that NA enhancing drugs increase the size of MEPs (see Table 3). This indicates that NA has a facilitatory effect on human motor cortical and/or spinal motoneuronal excitability. Importantly, in healthy participants, noradrenaline reuptake inhibitors (NRIs) such as atomoxetine and reboxetine that selectively increase the synaptic concentration of NA increase resting MEP amplitude (Kuo et al., 2017b; Plewnia et al., 2002, 2004; Sczesny-Kaiser et al., 2014), indicating that increases in motor system excitability can be caused by NA alone and not merely in combination with reuptake inhibition or facilitation of other neurotransmitter systems. For example, some studies indicate that noradrenaline dopamine reuptake inhibitors (NDRIs, i.e., methylphenidate) and amphetamine also increase resting MEPs in healthy subjects (Boroojerdi et al., 2001; Ilic et al., 2003). It also appears that both single dose and chronic administration of an NRI both increase resting MEP amplitude, and hence drug-effects on the MEP do not depend on the number of administrations (i.e., longer term use, as seen with SSRIs).

Antagonism of the Gi/o coupled α_2 receptor with yohimbine increases resting MEP amplitude (Plewnia et al., 2001). NA producing neurons express α_2 receptors, and these pre-synaptic α_2 receptors act to decrease extracellular concentrations of NA through a negative feedback loop (Philipp et al., 2002). With drug administration, α_2 receptor antagonism hinders this negative feedback mechanism to promote increases in extracellular NA concentrations. This is perhaps why α_2 antagonists and NRIs both increase MEP amplitude and activating α_2 receptors with the agonist guanfacine, which will act to reduce extracellular concentrations of NA, has the opposite effect, and reduces resting MEP size (Korchounov et al., 2003). Noradrenergic effects on the MEP are not limited to the α_2 receptor, as antagonism of the Gq coupled α_1 receptor with prazosin has also been shown to increase the size of resting MEPs (Korchounov and Ziemann, 2011). Yet, MEPs were not affected by the β receptor antagonist propranolol in any study we found (Nitsche et al., 2004; Sawaki et al., 2003).

Overall, motor threshold was not affected by NA drugs (Boroojerdi et al., 2001; Buchmann et al., 2006, 2007, 2010; Butefisch et al., 2002; Foster et al., 2006; Gilbert et al., 2006a, 2007; Hoeppner et al., 2008; Ilic et al., 2003; Kesar et al., 2017; Kirschner et al., 2003; Korchounov et al., 2003; Kratz et al., 2009; Kuo et al., 2017b; Lange et al., 2007; Meintzschel and Ziemann, 2006; Moll et al., 2000, 2003; Ozdag et al., 2010; Plewnia et al., 2001, 2002, 2004; Sawaki et al., 2002, 2003; Schneider et al., 2011; Sczesny-Kaiser et al., 2014; Ziemann et al., 2002), except for a single study showing a decrease in RMT with the NRI reboxetine (Herwig et al., 2002). Thus, consistent with the 5-HT system, the NA system has minimal effects on TMS-activated lower threshold cortical circuits that project to motoneurons or the excitability of lower-threshold motoneurons.

3.2. Noradrenaline increases intracortical facilitation and reduces inhibition

Under conditions of pharmacologically heightened NA neurotransmission, increases in the size of MEPs could be the consequence of increased intracortical facilitation and/or a decreased intracortical inhibition. As can be seen in Table 3 there are several studies where noradrenergic enhancing drugs simultaneously increase ICF and decrease SICI in healthy individuals (Boroojerdi et al., 2001; Gilbert et al., 2006a; Herwig et al., 2002; Ilic et al., 2003; Kirschner et al., 2003; Kuo et al., 2017b; Moll et al., 2003; Plewnia et al., 2002, 2004; Sczesny-Kaiser et al., 2014). Hence, noradrenergic neurotransmission appears to both augment intracortical facilitatory activity and suppress inhibition to increase motor cortical excitability.

With respect to ICF, a subthreshold facilitatory circuit may be augmented by NA. Specifically, enhanced noradrenergic transmission with drug administration perhaps increases the output of excitatory interneurons or increases the responsiveness of corticospinal neurons to excitatory input. The α_2 receptor can be linked to NA effects on ICF, whereby blocking the α_2 receptor with yohimbine increases ICF (Plewnia et al., 2001), and activation of the α_2 receptor with the agonist guanfacine reduces ICF (Korchounov et al., 2003). Perhaps, as the pre-synaptic α_2 receptor acts to reduce extracellular NA concentrations (Philipp et al., 2002), drugs that target this receptor are simply controlling the availability of NA in the synapse and ICF effects are instead mediated by post-synaptic receptors. Yet, α_1 (prazosin) and β receptor (propranolol) antagonists do not affect ICF (Sawaki et al., 2003). Regarding SICI, enhanced NA activity could reduce the output or efficacy of inhibitory cortico-cortical projections that act on corticospinal projections to motoneurons. Pharmacological activation of the α_2 receptor increases SICI (Korchounov et al., 2003), possibly by reducing synaptic NA concentrations as explained above. Like α_1 and β antagonist effects on ICF, α_1 and β receptor antagonists do not affect SICI (Sawaki et al., 2003).

The administration of NRIs and NDRIs have been shown to enhance SICI, and hence estimates of intracortical inhibition, in individuals with attention-deficit/hyperactivity disorder (ADHD), albeit paired pulse TMS results are not entirely consistent between studies involving this population (Buchmann et al., 2007; Gilbert et al., 2006b, 2007; Moll et al., 2000; Schneider et al., 2011). LICI is reduced with chronic methylphenidate (an NDRI) administration in healthy participants (Buchmann et al., 2010), but LICI is increased with chronic methylphenidate administration in individuals with ADHD (Buchmann et al., 2007). The TMS-induced silent period is not affected by any NA drug in healthy participants or in individuals with ADHD (Hoeppner et al., 2008; Ilic et al., 2003; Klass et al., 2012, 2016, 2018; Korchounov et al., 2003; Moll et al., 2000, 2003; Ozdag et al., 2010; Sawaki et al., 2003). Considering that NA drugs affect SICI and LICI but not the TMS-induced silent period, this could indicate that the inhibitory mechanisms or circuits that condition a MEP are likely distinct to inhibitory mechanisms causing the TMS-induced silent period.

3.3. Noradrenergic effects on spinal motoneurons

We identified several studies examining NA drug effects on motoneuron excitability (Boroojerdi et al., 2001; Brunia, 1972, 1979; De and Richens, 1974; Ilic et al., 2003; Klass et al., 2016, 2018; Korchounov et al., 2003; Mai, 1978; Mai and Pedersen, 1976; Phillips et al., 1973; Plewnia et al., 2001, 2002; Udina et al., 2010; White and Richens, 1974). Although we did not find one instance where cervicomedullary

stimulation was used to assess human motoneuron excitability changes after the administration of NA drugs (Table 3), drugs that enhance NA activity (i.e., amphetamines, NRIs) increase the size of H-reflexes and stretch reflexes in healthy participants (Brunia, 1972; Klass et al., 2018; Phillips et al., 1973). This indicates that NA increases human motoneuron excitability to sensory afferent input.

The post-synaptic facilitatory effects of NA on human motoneuron excitability are probably mediated by the somato-dendritic α_1 receptor, as blocking the α_1 receptor with thymoxamine or indoramin reduces stretch reflexes in healthy participants (De and Richens, 1974; Phillips et al., 1973) and reduces both H- and stretch reflexes in individuals with brain and spinal injuries (Mai, 1978; White and Richens, 1974). Vibratory reflexes are also reduced by the α_1 receptor antagonist thymoxamine (Mai, 1978). These findings align with animal work, whereby α_1 receptor agonists cause large increases in motoneuron excitability in the cat and rat (Lee and Heckman, 1999; Rank et al., 2011). It should be noted that increased extracellular concentrations of NA can cause the augmented activation of both α_1 and α_2 receptors at both pre- and post-synaptic sites. In addition to facilitatory α_1 receptors on motoneurons, inhibitory α_2 receptors are located on sensory afferents and reduce sensory afferent transmission to motoneurons (D'Amico et al., 2014; Rank et al., 2011). Considering that NA enhancing drugs increase the excitability of motoneurons to sensory afferent input, it could be likely that α_1 receptor mediated increases in motoneuron excitability override parallel reductions in sensory transmission mediated by the inhibitory pre-synaptic α_2 receptor.

Consistent with an excitability reducing effect for the α_2 receptor at a spinal level, activation of the α_2 receptor with the agonist clonidine reduces the size of stretch reflexes (De and Richens, 1974). There are two possibilities that could explain how α_2 receptor activation with clonidine reduces the size of muscle responses to sensory afferent input. As explained above, the reduction in stretch reflexes with α_2 receptor activation could be a consequence of reduced sensory transmission to motoneurons (D'Amico et al., 2014; Rank et al., 2011). On the other hand, activation of pre-synaptic inhibitory α_2 auto receptors on NA releasing neurons could reduce NA concentrations in synapses (Philipp et al., 2002), meaning NA would be less able to activate post-synaptic α_1 receptors at motoneurons that act to enhance motoneuron excitability.

Interestingly, an isolated study indicates that β receptor antagonism with propranolol may increase the size of stretch reflexes in healthy participants (Brunia, 1979), suggesting that this receptor augments the excitability of a component/s of the spinal sensorimotor loop. Yet, NA drugs such as NA stimulants (amphetamine), NRIs and NDRIs (reboxetine, methylphenidate), and α_2 receptor antagonists and agonists (yohimbine, guanfacine) do not affect F-waves (Boroojerdi et al., 2001; Ilic et al., 2003; Korchounov et al., 2003; Plewnia et al., 2001, 2002), indicating that the recurrent discharge of human motoneurons to antidromic activation is not affected by this neuromodulator. It is important to note, however, that F-waves may not always be a sensitive test to identify changes in motoneuron excitability (Balbi, 2016; Lin and Floeter, 2004), so it is not unusual for F-waves to remain unaffected by interventions that affect other measures of motoneuron excitability such as H-reflexes or CMEPs. Specifically, an increase/decrease in motoneuron excitability may not always result in corresponding increases/decreases in F-wave amplitude or persistence (Balbi, 2016), and the mechanisms that generate the recurrent discharge of motoneurons to antidromic activation are still becoming increasingly known (Özyurt et al., 2023), both precluding a strong interpretation of F-waves in a neurophysiology context.

4. Drugs with combined serotonin and noradrenaline effects support a role for monoamines in the excitability of motor pathways

Table 4 summarises the results of studies that used a drug intervention targeting both NA and 5-HT reuptake or used antagonists with a strong affinity for both 5-HT and NA receptors (Basmajian and Szatmari, 1955; Brunia, 1973; D'Amico et al., 2013b; De and Richens, 1974; Foster et al., 2006; Li et al., 2018; Li and Morton, 2020; Lissemore et al., 2021; Metz et al., 1982; Munchau et al., 2005; Stern et al., 1968). A notable finding was that combined α_2 and 5-HT_2 receptor antagonism with mirtazapine lengthens the TMS-induced silent period in healthy participants without affecting motor threshold, unconditioned and conditioned MEPs (Munchau et al., 2005). Considering that the more selective 5-HT_2 antagonist cyproheptadine also lengthens the TMS-induced silent period (Thorstensen et al., 2021), but a drug selectively targeting the α_2 receptor (guanfacine) has no effect on the same outcome (Korchounov et al., 2003), the 5-HT_2 receptor effects of the drug could explain this result. To this end, the effects of the 5-HT_2 receptor on the cortical silent period provides further support for a role of 5-HT in intracortical inhibition. Combined α_2 and 5-HT_2 receptor antagonism lowers AMT in individuals with co-occurring depression and epilepsy but has no effect on single and paired pulse MEPs or the TMS-induced silent period in this population (Munchau et al., 2005). At the level of the spinal cord, combined α_1 and 5-HT_2 antagonism with the neuroleptic medication chlorpromazine tends to reduce the size of H- and stretch reflexes (Basmajian and Szatmari, 1955; Brunia, 1973; De and Richens, 1974; Stern et al., 1968), providing further support that 5-HT and NA acts via α_1 and 5-HT_2 receptors to increase motoneuron excitability in humans.

5. Considerations

Several of the studies included in this review use drugs that have strong affinities for other receptors outside of their primary pharmacological target, and this makes it difficult to understand the specific neuromodulator/s driving post-drug changes in motor cortical and spinal motoneuronal excitability. Along these lines, although many of the drugs mentioned in this review largely target a single neurotransmitter system or receptor, it is important to reiterate that it is not always possible to classify drugs based on a single pharmacologic effect. For example, buspirone is both an agonist at 5-HT_{1A} receptors and an antagonist of dopamine D_2 receptors, cyproheptadine has antihistamine and anticholinergic properties in addition to its 5-HT_2 antagonist properties, and chlorpromazine is a D_2, α_1 and 5-HT_2 receptor antagonist. Likewise, many of the noradrenergic drugs included in Table 3 also have strong effects on dopaminergic neurotransmission. It is also important to consider that some drugs have active metabolites, which may also exert neuroactive effects after single-dose or chronic administration, and individual drugs from the same drug class have different pharmacological profiles (e.g., the pharmacology of SSRI medications like paroxetine and citalopram differ). Regarding the latter, this may confound the ability to make comparisons between studies using different drugs from the same drug class.

It is likely that drug effects on motor cortical and spinal motoneuron excitability outcomes scale in magnitude with the drug dose. Accordingly, if a particular drug at a given dose does not cause a significant change in corticospinal or motoneuronal excitability, this does not necessarily mean that the associated neuromodulator or receptor has no effect on that outcome, it might be that a particular dose of drug is not sufficient to cause detectable effects across a sample of participants.

Although extensive, our search strategy to identify studies was not technically systematic, and we cannot discount the possibility that there are additional human studies that investigated 5-HT and NA drugs on motor cortical and/or spinal motoneuronal excitability.

6. Behavioural inferences

Animal studies can help elucidate the relevance of monoaminergic neurotransmission and the behaviours that cause monoamine release to the motor system. Extracellular recordings from the brainstem show that the firing rates of descending raphe 5-HT producing neurons align with the speed of locomotion in cats (Jacobs et al., 2002; Veasey et al., 1995),

whereby faster locomotion results in faster firing rates and 5-HT release to the spinal cord and motoneurons. Considering this, and the results of our review indicating a facilitatory effect of 5-HT on human motoneuron excitability (under conditions without muscle fatigue, Table 2), it seems likely that a primary function of the descending 5-HT system is to increase motoneuron excitability during strong motor behaviours requiring significant output from the corticospinal pathway and motoneurons (e.g., during movements requiring strong motor outflow to muscle). Under these conditions, it is entirely likely that the purpose of large 5-HT release to the cord is to increase motoneuron excitability and make it easier for descending ionotropic pathways to recruit motor units and maintain their discharge with minimal excitatory drive.

The most prominent collection of NA cells forms the pontine locus coeruleus (Berridge and Waterhouse, 2003; Poe et al., 2020). The tonic discharge activity of locus coeruleus noradrenergic neurons is scaled to the level of arousal, whereby there are low to moderate firing rates during quiet waking but fast firing rates upon conditions that require high arousal (Berridge et al., 2012; Berridge and Waterhouse, 2003). This indicates that NA release to the brain and spinal cord is augmented during states of high alertness, stress, or anxiety, i.e., during behaviours that are associated with a heightened activation of the sympathetic nervous system. Perhaps, as NA enhancing drugs increase the excitability of the human motor cortex and motoneurons (Table 3), and NA release is large with heightened sympathetic activity, we suggest that NA circuits are needed to strengthen the output of the motor cortex and motoneurons under conditions of hyperarousal (colloquially labelled 'fight or flight' conditions). From an evolutionary standpoint, the gain of the motor system may be augmented to quickly activate muscle and escape a predator when we want to 'flight', and more powerfully activate muscle when we need to 'fight'.

Notably, both 5-HT and NA producing cells are quiescent during rapid eye movement (REM) sleep (Berridge and Waterhouse, 2003; Jacobs et al., 2002), a stage of sleep characterised by reductions in muscle tone and a complete suppression of motor output. Consistent with our above suggestions, this makes sense. High levels of neuromodulation of the motor system and the enhanced excitability of motoneurons are not needed at complete rest when skeletal muscle activation is not needed. Alternatively, in a waking state, 5-HT and NA projections could serve as a tonic controller of the motor system to maintain background muscle tone, and 5-HT (for strong motor outflow) and NA (with high stress situations) release upregulated when required.

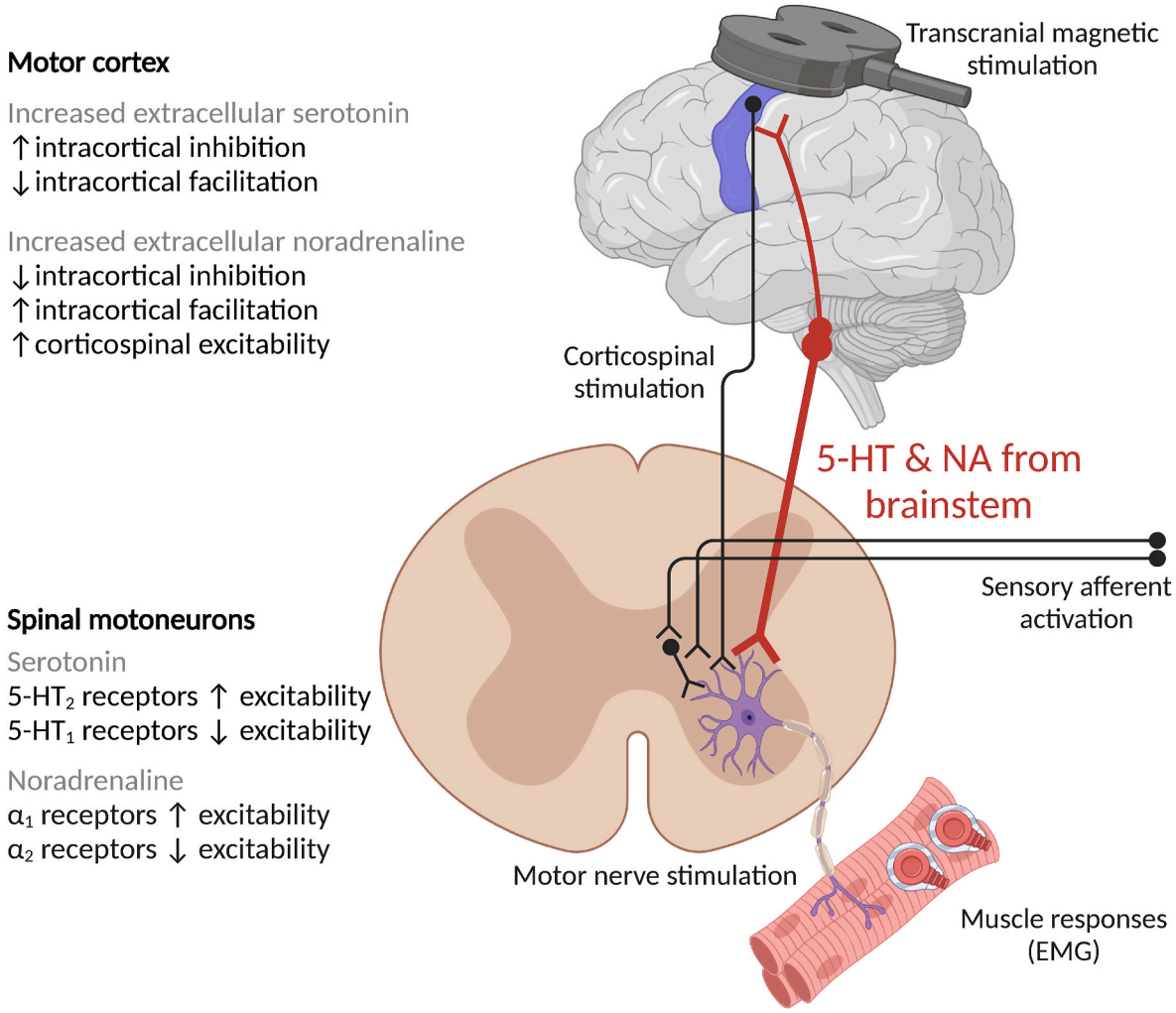

Fig. 1. Schematic summarising the main take home findings from this review. Overall, it appears that enhanced extracellular concentrations of serotonin (5-HT) and noradrenaline (NA) decrease and increase the excitability of the human motor cortex respectively, but it is not quite clear what receptors mediate these changes in excitability at a cortical level. At a spinal level, 5-HT and NA tend to increase the excitability of spinal motoneurons in humans, which is mediated by post-synaptic 5-HT_2 and α_1 receptors on motoneurons. On the contrary, pre-synaptic 5-HT_1 and α_2 receptors on sensory afferents, spinal interneurons or 5-HT and NA releasing neurons can reduce sensory transmission to motoneurons or decrease 5-HT/NA concentrations in the synapse, and post-synaptic 5-HT_1 receptors reduce motoneuron excitability. It should be noted that this figure simplifies complex supraspinal and spinal circuits involving excitatory, inhibitory, and neuromodulatory inputs and is not intended to be all-inclusive. Created with BioRender.com.

7. Summary and future directions

We were interested in collating studies examining the effects of monoaminergic drugs on the excitability of the human motor cortex and motoneurons, as these studies best indicate whether a particular monoamine system or receptor can be implicated in motor cortex and/or motoneuron function. Indeed, human drug studies tell us that both 5-HT and NA neurotransmission greatly affect the excitability of the motor system at both cortical and spinal levels. Yet, considering that most of the studies included in this review involved resting measurements of motor cortical and/or motoneuronal excitability, i.e., when participants are sitting in a controlled lab environment in a relaxed state, these studies do not provide much insight regarding the behaviours that cause 5-HT and NA release in the human brain and spinal cord. Therapeutic doses of monoaminergic drugs simply mimic or 'knockout' the normal physiological effects exhibited by 5-HT and NA to enhance or reduce the effects of a particular transmitter system (compared to a condition without a drug). There needs to be a better effort in future human drug studies to explore the behaviours that cause 5-HT and NA release in the brain and spinal cord, and the resultant functional effect/s that monoamine release has on the output of motor pathways.

The key take home message from this review is that the monoaminergic neuromodulators 5-HT and NA have strong effects on the excitability of the human motor cortex and motoneurons. Fig. 1 provides a graphical overview of the effects of 5-HT and NA in the human motor cortex and at spinal motoneurons. When TMS is used to test the excitability of motor cortical circuits, drugs that enhance 5-HT activity tend to reduce measures of facilitation and augment measures of inhibition, indicating that 5-HT acts to reduce intracortical excitability. Conversely, NA promoting drugs have the opposite effects, markedly increasing motor cortical excitability across many studies and populations, whereby the pharmacological enhancement of NA activity increases paired-pulse TMS measures of intracortical facilitation and reduces measures of inhibition. Considering that TMS of the motor cortex assesses the excitability of the entire corticospinal-motoneuronal system from the cortex to muscle, 5-HT and NA drugs could have acted at motoneurons to cause these excitability changes. Indeed, drug studies indicate that 5-HT has powerful effects on human motoneurons, whereby 5-HT enhancing drugs increase motoneuron excitability through 5-HT_2 receptor activation, but activation of 5-HT_1 receptors may also reduce human motoneuron excitability under specific conditions (i.e., with fatiguing muscle contractions) or reduce sensory transmission to motoneurons. Likewise, NA enhancing drugs increase the excitability of human motoneurons to synaptic input, and it is likely that the facilitatory effects of NA on human motoneuron excitability are mediated by α_1 receptors.

Hopefully this review brings to attention a role for endogenously released monoamine neuromodulators in the function of motor circuits in the human brain and spinal cord. Overall, additional human investigations are required to aid in the understanding of how these monoamines control the excitability of the human motor cortex and motoneurons in health and disease.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Author contributions

Jacob Thorstensen: Conceptualisation, literature review and creation of tables, writing, editing. Tyler Henderson: Conceptualisation, editing and feedback. Justin Kavanagh: Conceptualisation, editing and feedback.

Declaration of competing interest

None to declare.

Data availability

No data was used for the research described in the article.

Acknowledgements

There are no acknowledgements to declare.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neuropharm.2023.109761.

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