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Genetics, molecular control and clinical relevance of habituation learning.

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1. Contents

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2. Abstract

Habituation, the most ancient and fundamental form of learning, manifests already before birth. Neuroscientists have been fascinated for decades by its function as a firewall protecting our brains from sensory information overload and its indispensability for higher cognitive processing. Evidence that habituation learning is affected in autism and related monogenic neurodevelopmental syndromes and their animal models has exponentially grown, but the potential of this convergence to advance both fields is still largely unexploited.

In this review, we provide a systematic overview of the genes that to date have been demonstrated to underlie habituation across species. We describe the biological processes they converge on, and highlight core regulatory pathways and repurposable drugs that may alleviate the habituation deficits associated with their dysregulation. We also summarize currently used habituation paradigms and extract the most important arguments from literature that support the crucial role of habituation for cognition in health and disease. We conclude that habituation is a powerful tool to overcome current bottlenecks in research, diagnostics and treatment of neurodevelopmental disorders.

3. Introduction

3.1. Habituation learning

Habituation, the response decrement to a repeated irrelevant stimulus, is a fundamental form of learning that is conserved across the animal kingdom. It represents an essential filter mechanism that helps to identify salient signals in the environment by reducing the transmission of previously encountered stimuli to high-order brain regions. This allows organisms to distinguish the known from the novel, prevents information overload, and preserves cognitive resources for important matters. Habituation is the earliest form of learning that manifests before birth [1-6]. Its properties make it an important prerequisite to acquire higher cognitive

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functions [9,15-19]. In agreement with its fundamental role in cognition, infant habituation has been found to predict later IQ better than standardized measures [1-7], and deficits in habituation have been linked to several cognitive disorders [8-10].

The strong evolutionary conservation of habituation learning allows researchers to use animal models to dissect the genetic and neuronal mechanisms and study habituation deficits that are associated with human disease. Such insight from animal models may help to elucidate disease mechanisms, identify which individuals are more likely to have defective habituation in (genetically) heterogeneous disease cohorts and stratify patients for targeted pharmacological treatment strategies. In addition to conventional rodent models such as mouse (*Mus musculus*) and rat (*Rattus norvegicus*), research in cost and time-efficient organisms such as the zebrafish (*Danio rerio*), the fruit fly (*Drosophila melanogaster*), and the roundworm (*Caenorhabditis elegans*) has generated major insights into the neuronal and genetic mechanisms of habituation in health and disease.

3.2. Habituation paradigms

There is a wide range of paradigms available and used to measure habituation in pre-clinical and clinical settings. These paradigms differ in the type of the presented stimulus and of the response measured, while the defining characteristics of habituation are thought to be shared between various models and paradigms. These include, in addition to the response decrement to repeated presentation of the same stimulus (habituation): spontaneous recovery, recovery of the response when stimulus is changed (stimulus specificity), and recovery when a novel stimulus is inserted in the series of habituating stimuli (dishabituation) [11, 12]. The most commonly used habituation paradigms in humans and other organisms are listed in **Table 1,** and the latter further discussed in section 5.3.

3.3. Habituation mechanisms

The mechanisms underlying neuronal habituation are incompletely understood. Three main theories, originated decades ago, are perceived to be relevant. First, the “Stimulus-model

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comparator" theory, where repeated stimulation generates a model that is compared to the expected stimulus model, and the response is attenuated if the models match [13, 14]. Second, the "Sometimes opponent processes" theory, an adaptation of the Gnostic unit theory, where the generation of the stimulus-specific neuronal model activates inhibition of an arousal system [15, 16]. Third, the "Dual-process theory", where interaction between sensitization and habituation in the stimulus-response pathway defines the final response to the stimulus [17]. The principle elements of these theories were recently embodied in a generalizable habituation model that defines an essential set of operating elements required for habituation (a stimulation–receiver pair and the habituation element) and can also be applied to aneural forms of habituation. According to this model, repeated stimulation modifies the receiver output through time- and stimulus-dependent changes in the habituation element, thereby mediating habituation [18]. An equivalent of the "habituation element" is required in all three described neuronal habituation theories but its cellular and molecular basis remains abstract.

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Table 1: The most commonly used behavioral and physiological methods to assess habituation across organisms. *Since the early stages of research into habituation (see **[19]** for a review on the history of the term "habituation" and habituation research), a range of paradigms to assess habituation in different organisms, from worms to humans, have been developed. Some of the most commonly applied approaches to assess habituation are listed. They use physiological or behavioral read-outs.*

Startle reflex habituation uses startle-inducing stimuli to determine the reduction in response strength or response probability over repeated stimulation [20-23]. A commonly used stimulus is the acoustic startle stimulus (i.e. presentation of a loud tone; acoustic startle reflex (ASR) habituation), but visual, olfactory and somatosensory stimuli are also employed. In humans, the response output is most often a measure of blinking through Electromyographic (EMG) recording of the orbicularis oculi muscle. In animal models ranging from worms to rats, the output measure in this assay is also often a muscle or movement response to the startle stimulus. For example, the startle response in rodents is often quantified as the force the animal exerts by extension of its limbs onto a pressure-sensitive force transducer.
Visual habituation, which is also referred to as habituation of looking time, is used in rats and humans [24, 25]. In this habituation paradigm, test subjects are repeatedly presented with an auditory or visual stimulus (e.g. a real object or digital picture) and habituation is determined as a decrease in orienting response or fixation time to the presented stimulus. While in humans this paradigm is mostly applied in infants as part of the Visual Recognition Memory task [26], it has been succesfully used to study adults with even profound Intellectual Disability (IQ < 20/25) [27].
Electrodermal activity (EDA) habituation is also referred to as electrodermal response (EDR) habituation, event-related skin conductance response (SCR) habituation, or skin conductance orienting response (SCOR) habituation [28-32], or, previously, as Galvanic Skin Response (GSR) habituation [33]). In this paradigm, simple auditory, visual, or somatosensory stimuli are presented while measuring changes in the probability or magnitude of skin conductance with repeated stimulation. A decrease in probability or magnitude of the response represents habituation. EDA is performed in humans and various mammalian animal models.
In **Event-related potential (ERP) habituation,** the test subjects are exposed to a repeated stimulus, while undergoing electroencephalography (EEG), either using an electrode cap in humans or cranially implanted electrodes in animals. Habituation is described as a decrease in various components of the ERP wave's latency or amplitude [34-37]. It can assess different brain regions, according to the position of the electrodes. A variety of different stimuli including simple auditory, visual and somatosensory stimuli, nociceptive stimuli, complex auditory or visual stimuli (like speech or faces), as well as startling stimuli are used.
Functional Magnetic Resonance Imaging (fMRI) habituation can assess habituation of specific brain regions (e.g. amygdala habituation; [38, 39]) in humans and rodents rats [40]. In this paradigm, participants are presented with an auditory or visual stimulus (simple (e.g. tones or shapes) or complex (e.g. speech or emotional faces)), while an fMRI scanner records blood oxygen dependent (BOLD) contrast responses. A decrease in BOLD contrast with repeated stimulation represents habituation.
Novel object/environment habituation, frequently used in rodent habituation studies, but has no equivalent paradigms in humans or other model organisms. Within this paradigm a rodent is placed into a novel or known environment with a novel object in it. Habituation to the novel environment/object is defined as the amount of time the rodent is actively investigating the novel object, or as how long it takes the animal to present the "normal" behavior seen in a familiarized environment.
Open field habituation is solely employed in rodent habituation studies. Similar to the visual habituation paradigm, it makes use of rodents' innate behavior to explore new stimuli. Mice or rats are placed in an open field environment, and habituation is determined as the decrease in explorative behavior. This is most commonly measured as total distance traveled, and can be assessed over time within a session or over multiple sessions (i.e. intrasession or intersession habituation) [41, 42].

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Few years ago, before the definition of this generalizable habituation model, Mani Ramaswami highlighted the critical role for stimulus-dependent feedback inhibition [43]. He and colleagues experimentally demonstrated that odorant selective habituation in *Drosophila* relies on recurrent inhibitory potentiation of activated excitatory neurons [44-46]. Reviewing seminal electrophysiological studies of the *Aplysia* sifon withdrawal reflex that postulated homosynaptic depression of excitatory neurons as the mechanism of short-term habituation [47-49], he noted that even in this model with simple circuit organization (receptor neurons forming synapses with motor neurons), inhibitory potentiation is present [50, 51]. Inhibitory potentiation can better explain habituation characteristics that are difficult to reconcile with homosynaptic depression such as dishabituation, long-term habituation and that habituation is more effective with weak stimuli. Activity of inhibitory neurons can shape stimulus responses and habituation also in mammalian olfactory bulb [52, 53]. Because most brain regions consist of connected excitatory neurons that receive inhibitory input, Ramaswami proposed that any repeated excitatory stimulus can create an inhibitory signal (= negative image) of itself. The negative image neutralizes incoming signals of the expected stimulus pattern and strength, thereby acting as the selective filter that suppresses transmission to the downstream brain regions and/or behavior responses [43]. Inhibitory potentiation may thus represent a key mediator of habituation - the "habituation element" – operating across species, paradigms and brain regions. A neuronal algorithm implicating inhibitory potentiation of habituation should also be able to make predictions and efficiently detect salient features in the environment [54]. The "negative-image model" as defined by Ramaswami can thus serve as a general mechanism for adaptive filtering, generation of predictions and saliency mapping. Malfunctions of this mechanism are in line with – and may critically underlie - key features of Autism Spectrum Disorders (ASD), including sensory hypersensitivities, and information overload that arises from altered salience landscape [43, 55, 56]. The central molecular mechanism of recurrent inhibitory potentiation revealed by Ramaswami and colleagues is increased release of inhibitory neurotransmitter γ-

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aminobutyric acid (GABA) from inhibitory neurons in response to repeated stimulation. In short-term habituation, increased release of GABA is trigerred by Calcium/calmodulin-dependent protein kinase II (CamKII)-dependent phosphorylation of synapsin [45]. However, other additional kinases that are able to phosphorylate synapsin (ERK, PKA, CamKI) [57-59] may also be involved. Because inhibitory interneurons in the *Drosophila* olfactory response pathway are multiglomerular and their activation results in non-selective attenuation of the behavioral response, synapse-specific NMDA receptor activity in the principle excitatory neurons is required to allow for habituation to a specific odor [44]. Inhibitory-derived GABA then attenuates the activity of these neurons by binding to GABAA receptors [44]. Habituation is also dependent on cAMP activity in inhibitory neurons. While long-term habituation, most probably associated with changes in synaptic structure, employs cAMP-PKA-mediated activation of cAMP response element-binding protein (CREB), short-term habituation is CREB-independent [44] and is probably mediated only by short-term synaptic plasticity mechanisms.

4. A helicopter view on the molecular basis of habituation

Molecular players and mechanisms that are required for habituation can be further inferred from genetic studies in model organisms. Various approaches to identify genes that control habituation learning have been taken. These include unbiased forward genetic screens as well as reverse genetic approaches where animals with disruption of known genes were assessed for habituation deficits. Many of the latter focused on single genes, but a few went beyond. These efforts have been made by numerous research groups throughout years, and have not yet been compiled into a joined framework that contributes to a better understanding of habituation on the molecular level.

With this review, we aim to provide a systematic overview of all genes, and hence molecular players, that to date have been experimentally associated with decreased habituation.

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We further describe the biological processes and molecular pathways that these genes converge on and highlight core pathways that are subject to pharmacological targeting with promising drugs. Finally, we propose to apply habituation and the gained insights in pre-clinical disease models and in clinical trials to improve patient care for neurodevelopmental disorders.

4.1. A catalog of genes underlying habituation

To provide a comprehensive overview of the genes required for adaptive habituation responses, we systematically searched the PubMed database. The final search term string used to extract relevant publications that connect individual genes to habituation deficits is depicted in **Figure 1**. Excluded search terms (indicated by NOT) resulted from earlier searches that exclusively led to studies irrelevant for our aim. The final search string detected 679 publications that were manually screened by at least two of the authors on title and abstract for suitability. This initial screening resulted in the selection of 241 publications, which were viewed in full length. 118 of these provided at least one to many unambigous gene – habituation deficit pairs. Other publications measured but did not find habituation deficits in their genetic model(s), showed (or claimed) increased habituation, did not or not unambiguously target individual genes, or described paradigms that did not meet habituation criteria.

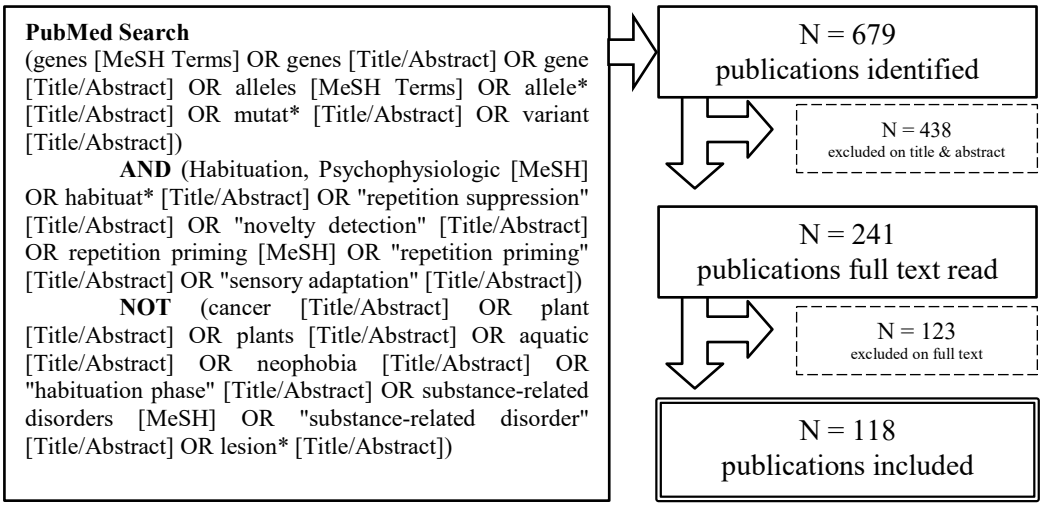

Figure 1. Flow chart depicting the search term and selection process of publications for inclusion into this review.

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For the 120 publications, the following aspects were annotated for each monogenic defect found to cause a habituation deficit (**Table S1**); 1. Original gene name in the specific species, 2. Species, 3. Effect on function (LoF, GoF, unknown), 4. Mutation (or manipulation), 5. Habituation paradigm, 6. Habituation paradigm details, 7. Reference (PubMed identifier, PMID), year of publication plus name of the first and last author.

In total, our literature review identified 356 hits causing reduced habituation learning, in total corresponding to 278 genes in several species (see below), summarized in **Table S1**. The majority of these 356 hits induce (predicted) loss of function (307 hits). 18 hits were reported to represent gain of function mutations, and for 31 hits the effect on protein function remained unclear. Our systematic search found experimental evidence that links genes to habituation deficits in six different organisms; *Homo sapiens* (human; N = 4 genes), and the model species *Rattus norvegicus* (rat; N = 4 genes), *Mus musculus* (mouse; N = 52 genes), *Danio rerio* (zebrafish; N = 37 genes), *Drosophila melanogaster* (fruit fly; N = 124 genes) and *Caenorhabditis elegans* (roundworm; N = 37 genes).

To compile a cross-species catalog of conserved genes linked to habituation deficits (i.e. genes implicated in habituation deficits in any or several of the six organisms) and allow subsequent gene ontology (GO) and pathway analyses, we next annotated the human orthologs of all genes identified in the five model organisms. We submitted the genes to the DRSC integrative ortholog prediction tool (DIOPT) that compiles evidence from 18 databases [60]. To include top-ranking orthologs, but exclude more distal homologs, we applied a number of criteria described in the legend of **Table 2**.

Of the 278 genes identified in the different species, 20 showed poor conservation, with the top-ranking genes having a DIOPT score below 3. These were considered as insufficiently conserved and excluded from further analyses, leaving us with a catalog of 258 evolutionary conserved genes to be matched across species.

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Due to one-to-many gene orthologies in *Drosophila* and *C. elegans*, frequently associating a single invertebrate gene to two or several human genes forming a related (potentially functionally overlapping or redundant) gene family, the conversion of the model organism gene catalog to human genes inflated the total number of genes from 258 to 421 genes. To illustrate the origin of this inflation, we assigned an inflation score to each organism, calculated as the number of human orthologs divided by the corresponding number of the originally identified genes in the respective species (**Table 2**). Mouse and Rat inflation score equals 1, reflecting exclusively one-to-one orthology. The inflation score of *Drosophila* is 1.87. Thus on average, each fly gene implicated in habituation led to the annotation of almost two paralogous human genes. *C. elegans* received the highest inflation score, 2.73, while zebrafish, due to a genome duplication event in teleost evolution, has an inflation score smaller than 1 (0.76).

Table 2. Demographics of the gene catalog and the inflation score linked to the conversion to human genes. For the conversion of species genes to human orthologs we utilized the DIOPT tool. All suggested orthologs with a DIOPT score of at least four were adopted if: 1. the ortholog was annotated with "Best score", 2. the ortholog belonged to the same gene family and had a comparable DIOPT score as the ortholog with the "Best Score" annotation, 3. the ortholog was the "Best reverse" and has a comparable DIOPT score to the "Best score" ortholog even if it did not belong to the same family, 4. the ortholog was annotated with "Best reverse" and is a known disease gene.

Organism	Publications	Hits	Genes	Human orthologs	Inflation score
H. sapiens	12	12	4	4	1.00
R. norvegicus	4	4	4	4	1.00
M. musculus	59	61	52	52	1.00
D. rerio	6	38	37	28	0.76
D. melanogaster	27	165	124	232	1.87
C. elegans	8	53	37	101	2.73

All genes required for habituation, the species they were identified in, the corresponding reference and their annotated human ortholog(s) are listed in **Figure 2**, in alphabetical order of the human gene name(s). Genes that have been implicated in habituation in more than one organism are highlighted in dark color and will be further refer to as multispecies hits, for simplicity. Two genes, *FMR1* and *SYNGAP*, have been associated with defective habituation in four out of the six depicted model organisms (human, mouse, fish, and fly). *GIGYF2* has been found to underlie habituation in three species (fish, fly and worm) and an additional 15 genes

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H. sapiens
(62) BDNF
(63-71) FMR1
(72) MAOA
(73) SYNGAP1

R. norvegicus
Cntnap2 (74) CNTNAP2
Dab1 (75) DAB1
Grin1 (76) GRIN1
Tsc1 (77) TSC1

M. musculus	
Bmal1 (78) ARNTL	Kcnma1 (106) KCNMA1
Atp1a2 (79) ATP1A2	Large1 (107) LARGE1
Atp1a3 (80) ATP1A3	Lsamp (108) LSAMP
Bsg (81) BSG	Nlgn3 (109) NLGN3
Casp3 (82) CASP3	Nr1d1 (110) NR1D1
CerS6 (83) CERS6	Nrg1 (111) NRG1
Chrm2 (84) CHRM2	OMP (112) OMP
Chrna6 (85) CHRNA6	Otx2 (113) OTX2
Ckap5 (86) CKAP5	Plat (114, 115) PLAT
Cln8 (87) CLN8	Ppargc1a (116) PPARGC1A
Clock (78) CLOCK	Prkn (117, 118) PRKN
Dgki (88) DGKI	Ptpra (119) PTPRA
Disc1 (89) DISC1	ptprr (120) PTPRR
Drd1 (90, 91) DRD1	Rag-1 (121) RAG1
Dtnbp1 (92, 93) DTNBP1	S100b (122, 123) S100B
Egr3 (94) EGR3	Shank3 (124) SHANK3
Epm2a (95) EPM2A	Slc6a3 (125) SLC6A3
Esr2 (96) ESR2	Srf (126) SRF
Fmr1 (97, 98) FMR1	Stat6 (127) STAT6
Cx36 (99) GJD2	Syngap1 (73) SYNGAP1
Gpr88 (100) GPR88	Tnc (128) TNC
Gria1 (101) GRIA1	Tph2 (129) TPH2
Grin1 (102) GRIN1	Unc5c (130) UNC5C
Grm5 (103) GRM5	(131) ACHE*
gtf2i (104) GTF2I	(132, 133) SNCA*
Immp2l (105) IMMP2L	(134, 135) HTT*

D. rerio	
akt3b (136) AKT3	mmp16a/b (136) MMP16
ap2s1 (137) AP2S1	nf1a/b (139, 140) NF1
cacna1c (136) CACNA1C	nr3c1 (141) NR3C1
cacnb2a/b (136) CACNB2	ntm (136) OPCML
chrm4a (136) CHRM4	pappaa (137) PAPPA
clcn3 (136) CLCN3	pcxa (137) PC
elfn1a/b (136) ELFN1	satb1a (136) SATB1
fmr1 (138) FMR1	sbno1 (136) SBNO1
gigyf2 (136) GIGYF2	shisa9a/b (136) SHISA9
gpm6aa/b (136) GPM6A	slc32a1 (136) SLC32A1
grin2aa/b (136) GRIN2A	syngap1a/b (136) SYNGAP1
ireb2 (136) IREB2	tcf4 (136) TCF4
kcna1a (137) KCNA1	tle3a/b (136) TLE3
mad1l1 (136) MAD1L1	zdhhc17 (137) ZDHHC17

D. melanogaster		
sax (142) ACVR1/L1	Lcch3 (153) GABRB1/2/3	Oga (162) OGA
rut (44, 143-145) ADCY1	Gad1 (142) GAD1/2	KrT95D (142) PACS1/2
Adk2 (142) ADK	Gale (142) GALE	Pak (142) PAK1/2/3
CG18012 (142) ALG1	Galt (142) GALT	CG1516 (142) PC
CG11851 (142) ALG9	simj (142, 157)^ GATAD2A/B	cp309 (142) PCNT;AKAP9
AP-1sigma (142) AP1S1/2/3	ppl (142) GCSH	dnc (142-144, 163) PDE4A/B/C/D
rb (142) AP3B1/2	Gdi (142) GDI1/2	Pex1 (142) PEX1
CG5316 (142) APTX	CG11148 (153) GIGYF1/2	CG6287 (142) PHGDH
RtGEF (142) ARHGEF6/7	Gyk (142) GK;GK2	PIG-V (142) PIGV
al (142) ARX	CG3999 (142) GLDC	row (142, 153, 164)^ POGZ
CG9510 (142) ASL	ci (142) GLI1/2/3	for (150, 165, 166) PRKG1
asp (142) ASPM	CG4270 (142) GLIPR2	CG6767 (142) PRPS1/1L/2
ATP7 (142) ATP7A/B	dally (142) GPC3/5	Pten (142) PTEN
XNP (142) ATRX	cin (142) GPHN	csw (142) PTPN6/11
Atx2 (146, 147) ATXN2/2L	CG3822 (142) GRIK1/2/3	Rab39 (142) RAB39A/B
BOD1 (148) BOD1	Nmdar2 (153) GRIN2A/B/C/D	CG42684 (153) RASAL2;DAB2IP;SYNGAP1
Blos1 (149) BLOC1S1	sgg (158) GSK3A/B	CG13690 (142) RNASEH2A
Raf (142) BRAF;ARAF;RAF1	Ih (142) HCN1/2/3/4	ssp3 (142) SCAPER
Ca-alpha1T (142) CACNA1G/H/I	Ras1 (142) HRAS;KRAS;NRAS	Prosap (142) SHANK1/2/3
Camta (150) CAMTA1/2	scu (142) HSD17B10	kar (142) SLC16A2/10
CASK (142, 151) CASK	Sh (159) KCNA1/2/3/4/5/6/7/10	CG1628 (142) SLC25A2/15
Dronc (142) CASP2	Hk (159, 160) KCNAB1/2/3	CG18347 (142) SLC25A18/22
Cbs (142) CASP2	Task7 (142) KCNK3/9/15	nac (142) SLC35C1
CG43370 (142) CC2D2A/B	slo (159, 160) KCNMA1;KCNU1	CG4300 (142) SMS
gek (142) CDC42BPA/B/G;DMPK	lid (142) KDM5A/B/C/D	usnp (142) SNAP29
CG13889 (142) CEP290	Hmt4-20 (153) KMT5B/C	Sos (142) SOS1;SOS2
Cep89 (152) CEP89	wb (142) LAMA1/2	Spred (142) SPRED1/2/3
Nrx-IV (150) CNTNAP1/2/3/3B/5	LanB2 (153) LAMC1/2/3	CG7280 (142) SUOX
Cog7 (142) COG7	CG12582 (142) MANBA	Syn (142) SYN1/2/3
CG5037 (142) COX10	Mek (142) MAP2K1/2	da (142, 143)^ TCF3/4/12
CG3925 (142) CRBN	MCPH1 (142) MCPH1	Tim8 (142) TIMM8A/B
hh (142) DHH;SHH;IHH	CG12118 (142) MMADHC	Tpi (142) TPI1
Dlg1 (142, 153)^ DLG1/2/3/4	Mocs2 (142) MOCS2	iav (163) TRPV6
su(r) (142) DPYD	CG14882 (142) MTRR	Tsc1 (142) TSC1
dysb (149) DTNBP1	Hem (153) NCKAP1/1L	UbcD6 (142) UBE2A/B
G9a (142, 154) EHMT1/2	Smr (153) NCOR1/2	pyd3 (142) UPB1
PEK (142) EIF2AK3	Nf1 (142) NF1	Upf3 (142) UPF3A/B
dom (153) EP400;SRCAP	Nrx-1 (142) NRXN1/2/3	CG8949 (142, 167)^ WAC
Xpd (142) ERCC2	Mes-4 (142) NSD1/2/3	bchs (153) WDFY3/4
CG15651 (142) FKRP	CG2277 (161) NT5DC1	Xpac (142) XPA
FoxP (142, 155) FOXP1/2/4	CG1814 (161) NT5DC2/3	zfh1 (142) ZEB1/2
Fmr1 (142, 156) FXR1/2;FMR1		

C. elegans
aps-2 (168) AP2S1
apl-1 (169) APP;APLP1/2
let-526 (168) ARID1A/B
unc-2 (168) CACNA1A/B/E
unc-36 (168) CACNA2D1/2/3/4
cmk-1 (170) CAMK1D/G;CAMK1;PNCK
cdkl-1 (168) CDKL1/2/3/4/5
unc-75 (168) CELF3/4/5/6
crh-1 (170) CREB1;CREM;ATF1
bar-1 (168) CTNNB1
dhp-1 (168) DPYS;DPYSL2/3/4/5;CRMP1
exc-7 (168) ELAVL1/2/3/4
cdh-4 (168) FAT1/2/3
C18H9.3 (168) GIGYF1/2
glr-1 (172-174) GRIA1/2/3/4
glr-2 (174) GRIA1/2/3/4
irx-1 (168) IRX1/2/3/4/5/6
kqt-1 (168) KCNQ2/3/4/5
jmjd-3.3 (168) KDM6A/B
set-16 (168) KMT2C/D
epi-1 (168) LAMA3/4/5
magi-1 (174) MAGI1/2/3
ogt-1 (170) OGT
pax-2 (168) PAX2/5/8
row-1 (168) POGZ
nab-1 (168) PPP1R9A/B
dkf-1 (168) PRKD1/2/3
hgap-1 (168) RALGAPA1/2
met-1 (168) SETD2
eat-4 (175) SLC17A6/7/8
unc-16 (168) SPAG9;MAPK8IP3
unc-18 (168) STXBP1/2/3
anc-1 (168) SYNE1/2
pop-1 (168) TCF7L1/2;TCF7;LEF1
unc-4 (168) UNCX
smg-4 (168) UPF3A/B
bra-1 (168) ZMYND8/11

Multispecies hit
Multi hit, monospecies
^ The results are from the same underlying data
* Mutated human transgene expressed in mice

Figure 2: Conserved genes causing reduced habituation upon manipulation. Genes are grouped by the organism in which they were investigated, and alphabetically ordered according to the name of the human ortholog. Depicted is the original gene name with the reference(s), followed by the human gene ortholog(s) as determined by the authors. Human orthologs supported by evidence in multiple species are highlighted in dark color (termed multispecies hit), while orthologs that are supported by multiple evidence in the same species are highlighted in light (monospecies multihit). ^ depicts results that have been reused by a second study. Since based on the same data these genes are not considered monospecies multihits. * indicates transgenic human alleles expressed in mice.

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have been found in two species (*AP2S1*, *CNTNAP2, DTNBP1, GRIA1, GRIN1, GRIN2A, KCNA1, KCNMA1, NF1, PC, POGZ, SHANK3, TCF4, TSC1, UPF3A/B*). 38 further genes are highlighted in light color. For these independent evidence for a role in habituation has been presented either by multiple models by the indicated reference or in two or more independent studies within the same species. These genes are referred to as monospecies multihit genes.

The compiled catalog contains genes with diverse protein functions. In the next section, we aimed to identify the biological processes that they contribute to, with a focus on signaling pathways that comprise multiple habituation genes and are druggable.

4.2. Gene Ontology

To identify molecular pathways and biological processes that are required for habituation learning, the compiled gene catalog was subjected to Gene Ontology (GO) analysis using AmiGO2 [175-178] (DOI: 10.5281/zenodo.4495804 Released 2021-02-01). To provide a broad overview on the biological processes identified by this analysis, we have limited the complexity of the outcome by combining functionally related individual GO term into compound GO terms [179]. The GO terms covered by the compound GO terms are described in detail in **Table S2**.

Figure 3 depicts 13 compound GO terms associated with large and/or very enriched gene groups. Together, they describe (one or more) biological functions of 290 human gene orthologs (i.e. for 73% of the identified 398 human genes). Genes that are connected only to a single of the 13 compound GO groups are shown (N = 152, 53%) on a dark background. Genes related to more than one compound GO term are depicted on a light background (N = 138, 47%). The six compound GO groups contributing the most genes associated only to a single compound GO group are included in a Venn diagram, highlighting that these processes are molecularly connected. Seven further compound GO groups are depicted separately, to limit complexity of the Venn diagram. These overlap very considerably with the genes already

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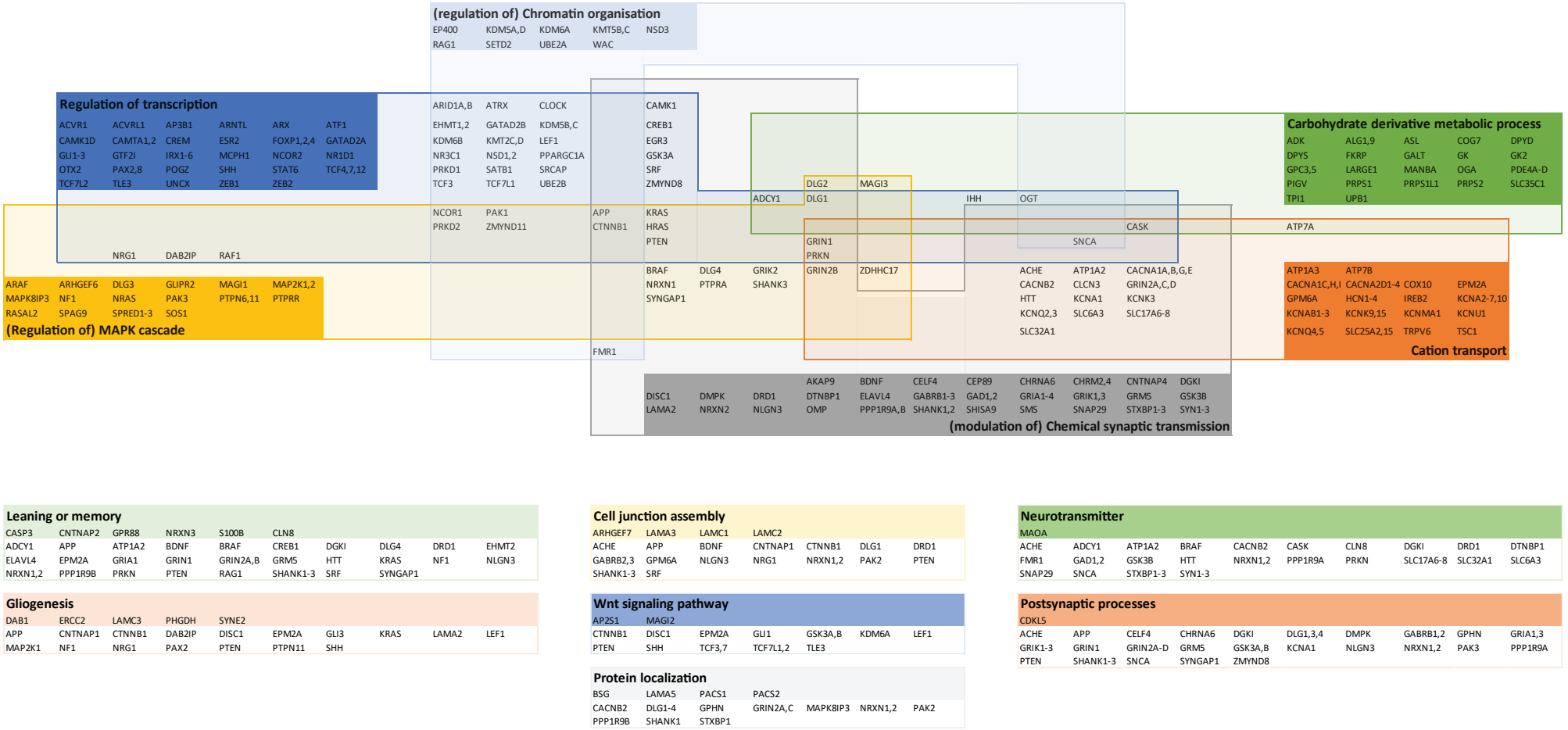

Figure 3: Venn diagram of compound GO terms describing biological processes linked to genes required for habituation. Compound GO terms represent functionally related GO terms (Table S2). The Venn diagram connects the 6 compound GO that contribute most genes only connected to a single compound GO term (dark background). Genes connected to multiple compound GO terms are shown on a light background.

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present in at least one other compound GO group and thus add in rather few genes only associated to a single compound GO group.

The Venn diagram highlights genes associated with the compound GO terms: Regulation of transcription (N = 91 genes | of which 35 associated with a single compound GO term), Cation transport (N = 65 | 35), Metabolic process (N = 35 | 27), MAPK cascade (N = 46 | 14), Synaptic transmission (N = 92 | 10) and Chromatin organization (N = 43 | 9). The genes operating in the largest number of represented biological functions are *APP* (associated with 8 of 13 compound GO terms), *PTEN* (8 of 13), *CTNNB1* (7 of 13), *DLG1* (7 of 13), and *NRXN1* (7 of 13).

It is not surprising that our gene list identifies biological processes related to synaptic transmission, learning or memory, postsynaptic processes, and neurotransmission; these are established biological processes linked to habituation learning. However, we also find biological processes such as the regulation of transcription, chromatin organization, metabolic processes, and Wnt signaling are well-represented. These processes are highly implicated in neurodevelopmental disorders [179, 180] and are at least in part known to regulate other forms of learning, but have not gotten much attention in relation to habituation learning. Additionally, we find biological processes related to cell junction assembly and gliogenesis, pointing to a contribution of neurodevelopmental components to habituation.

4.3. Molecular pathways and processes controlling habituation, and their drugability

Whereas the GO analysis provided an overview on the biological functions prominently involved in habituation, it does not capture all genes and, with the exception of MAPK and Wnt signaling, points to very broad processes. Not only with an eye to clinical applications, we found it worthwhile zooming in further to define additional molecular pathways in which genes required for habituation operate. Because of the large number of genes and space constrains, we in **Figure 4** focused on depicting those pathways and processes that aggregate a number of

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genes with strong evidence from multiple species (in red). These include (1) central cellular signal transduction cascades - PI3K-AKT-mTOR, Ras-MAPK, and cAMP-PKA (**Figure 4A**), (2) mechanisms of neuronal plasticity and excitability, in addition to these signal transduction cascades (**Figure 4B**), and (3) the control of protein translation (**Figure 4C**). Because these interconnected processes align well with the major mechanistic themes in neurodevelopmental disorders [181], they also are attractive targets for pharmacological intervention.

Because habituation learning as well as its genetic and molecular mechanisms appear to be deeply conserved, and small animals offer the opportunity to conduct drug testing *in vivo* at reasonable costs in bigger scale, such screens may uncover novel lead compounds. This has been impressively demonstrated by a compound screen that assessed the effect of 1760 compounds on acoustic startle habituation in wild-type zebrafish larvae [182]. 19 compounds were found to improve habituation learning. Most of these are targeting neurotransmitter systems, and eight are targeting disease mechanisms highlighted here, including intracellular signaling molecules (GSK3B, PKC, and PDE3), post-synaptic receptors (DRD and CHRM) and channels (CACNA1C) (**Figure 4**).

Figure 4D provides a synopsis of compounds either with a demonstrated positive effect on habituation (**Figure 4D**, left column) from the above or other studies, or a hypothetical suitability, based on targeting the depicted habituation-relevant pathways and evidence on the beneficial effect of these drugs for cognition (**Figure 4D**, right column). Many of these drugs are repurposable; 11 of them are approved by the U.S. Food & Drug Administration (FDA). Four additional drugs are currently being investigated in clinical trials. In the following subsections, these central habituation pathways and their drugability will be discussed further.

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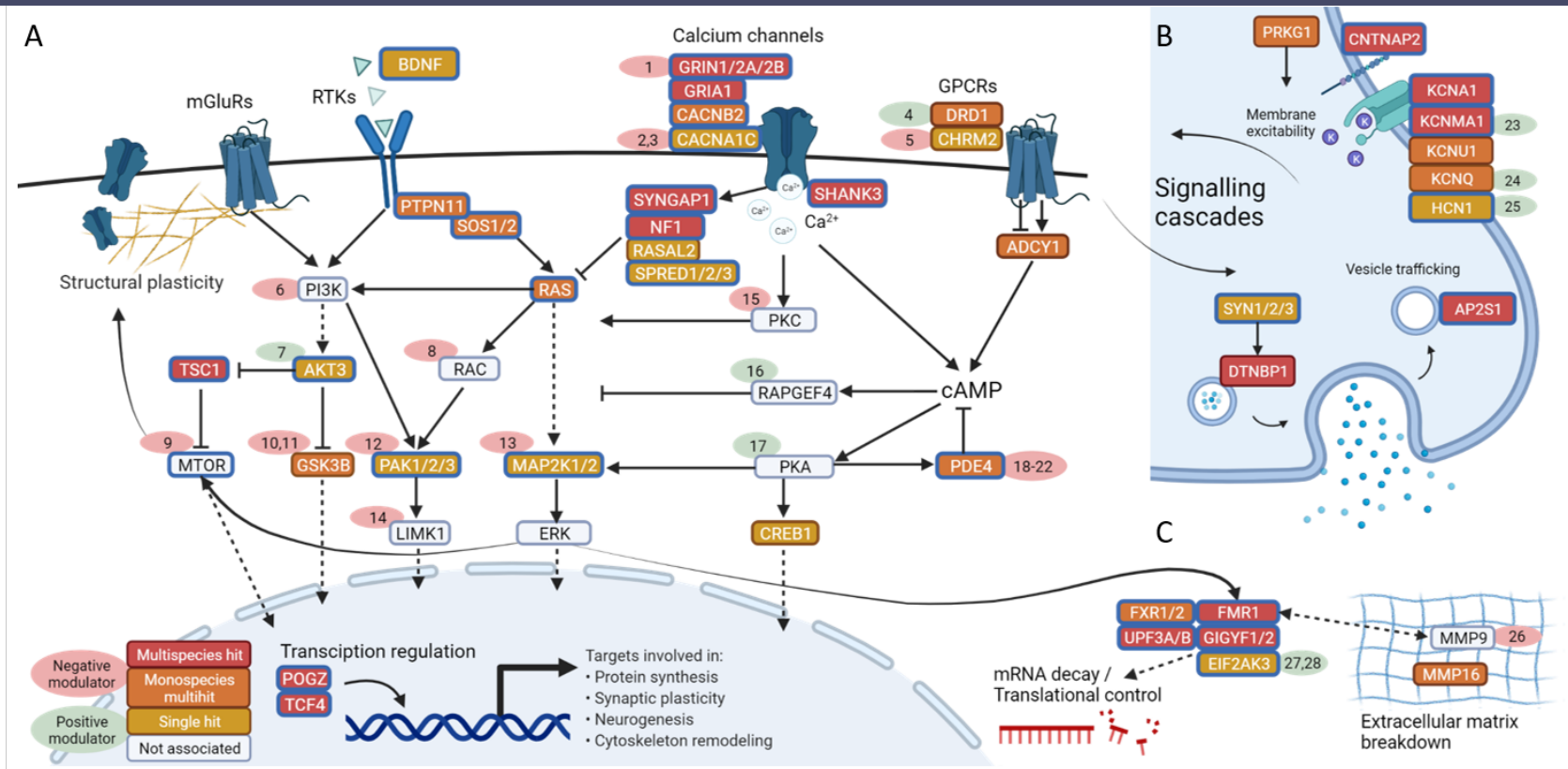

D

Drugs improving habituation learning

#	Drug	Target	Medical indication	Reference
1	Memantine	GRIN	Alzheimer's dementia*	68
2	Verapamil	CACNA1C	Hypertension*, cluster headache**	182
3	Nimodipine	CACNA1C	Neuroprotective after subarachnoid hemorrhage*	182
4	cis(+/−)-8-OH-PBZI hydrobromide	DRD3	-	182
5	Trihexyphenidyl hydrochloride	CHRM1	Parkinsonism*	182
10	Indirubin-3'-oxime	GSK3B	Alzheimer's***	182, 183
11	Kenpaullone	GSK3B	ALS***	182, 184
15	Chelerythrine chloride	PKC	Chemo-induced memory deficit***	182, 185
17	8-BR-cAMP	PKA	-	138
18	Olprinone hydrochloride	PDE3	Cerebral oxygen supply during surgery**	182, 186
19	Rolipram	PDE4	Depression**	138, 187
20	Roflumilast	PDE4	COPD*, cognitive impairment**	138, 188, 189
23	Flindokalner	KCNMA1	Fragile X***	190, 191
26	Minocycline	MMP16	Antibiotic*, neurodevelopmental disorders**	69

Drugs hypothetically improving habituation learning

#	Drug	Target	Medical indication	Reference
6	Buparlisib	PI3K	Cancers**	192
7	SC79	AKT	Cancers***, Alzheimer's***	193
8	EHop-016	RAC1	Cancers***, Alzheimer's***	194
9	Everolimus	mTOR	Cancers*, TSC (tumours and seizures)*	195, 196
12	IPA-3	PAK1	Cancers***	197
13	Selumetinib	MEK	NF1 (neurofibromas)*	198, 199
14	SR7826	LIMK	-	200
16	8-pCPT(-2'-O-Me-cAMP)	RAPGEF4	-	201
21	PF-04447943	PDE9	Alzheimer's**	202
22	Sildenafil	PDE5	Erectile dysfunction*, hypertension*	203
24	Ezogabine	KCNQ	Partial-onset seizures*, depression**	204, 205
25	Lamotrigine	HCN1	Bipolar disorder*, epilepsy*	206
27	CCT020312	EIF2AK3	-	207
28	Salubrinal	EIF2A	-	208

Figure 4. Schematic overview of the molecular processes and mechanisms comprising 17 of the 18 multispecies hits that are required for habituation. Not represented is PC (Pyruvate Carboxylase). The processes include **A.** PI3K-AKT-mTOR, Ras-MAPK, and cAMP-PKA pathways **B.** Synaptic plasticity and excitability and **C.** Translational control. **D.** Onto these processes we projected drugs **with experimental evidence** for their potential (left column), or which can be hypothesized to improve habituation learning; Monogenic causes of neurodevelopmental disorders [179] are highlighted with blue outline; *= FDA/EMA-approved, **= Off-label/clinical trials, ***= Only preclinical; ALS = Amyotrophic lateral sclerosis, COPD = Chronic obstructive pulmonary disease, TSC = Tuberous sclerosis complex, NF1 = Neurofibromatosis 1. Panels A.-C. were created using Biorender.com. Shown are gene not protein names, for simplicity.

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4.3.1. PI3K-AKT-mTOR, Ras-MAPK, and cAMP-PKA pathways

PI3K-AKT-mTOR and Ras-MAPK signal transduction cascades are key players of cell growth, proliferation, and cancer, but they also play a well-established, crucial role in neuronal development and synaptic plasticity. The cascades cross-talk at multiple levels (**Figure 4A**). Presynaptically, mTOR-dependent protein translation is important for growth and regeneration of axonal terminals. Postynaptically, activation of mTOR by N-methyl D-aspartate (NMDA) and metabotropic glutamate (mGluR) receptors increases local protein synthesis in dendrites contributing to structural plasiticity (reviewed in [209]). Phosphorylation of synapsin by ERK (Ras-MAPK) is required for presynaptic neurotransmitter release and hippocampus-dependent learning in mouse [210] (**Figure 4A,B**).

Germline mutations in the key players and their regulators of all three cascades are known to cause monogenic neurodevelopmental syndromes characterized by intellectual disability (ID) and, frequently, also ASD [181, 211]. Moreover, the baseline activity of PI3K-Akt-mTOR and Ras-MAPK is increased in idiopathic ASD cohorts and correlates with clinical severity [212]. In *Drosophila* light-off jump habituation, Ras-MAPK signaling is sensitive to opposing perturbation depending on the type of neuron. Increase of Ras-MAPK in inhibitory, GABAergic neurons and decrease of Ras-MAPK in excitatory, cholinergic neurons impairs habituation learning [141]. Partial loss of negative Ras-MAPK regulators SYNGAP1 and *NF1* are associated with habituation deficits in *Drosophila* and zebrafish. Using parallel EEG analysis approaches, SYNGAP1 mutations were shown to cause habituation deficits in mice and patients [72]. NF1 haploinsufficiency causes Neurofibromatosis type 1 (NF1), a genetic disorder with high frequency of ID and ASD. Deficits in long-term habituation in the zebrafish NF1 model were successfully rescued with drugs that inhibit MAPK (U0126), or PI3K (Wortmannin and Buparlisib) activity. Deficits in short-term habituation were rescued by drugs that enhance cAMP, including 8-BR-cAMP, Rolipram, and Roflumilast [138]. Furthermore, post-hoc assessment of four combined trials evaluating the MEK inhibitor Selumetinib in

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treating *NF1*-associated neurofibromas suggests no adverse and some beneficial effects on cognitive readouts [199].

cAMP acts as a second messenger in numerous signal transduction pathways. In neurons, an increase of cAMP levels is triggered by binding of neurotransmitters to G-protein coupled receptors, and by increased calcium influx. cAMP-activated PKA phosphorylates SNARE regulatory proteins and synapsins, which leads to enhanced synaptic vesicle release [213, 214] (**Figure 4B)**. Transcriptional regulation by cAMP-PKA signaling is mediated by the cAMP response element-binding protein (CREB). Thes orchestrated transcriptional programs are required for structural plasticity and memory consolidation [215]. cAMP in local GABAergic interneurons of the *Drosophila* antennal lobe is required for both short- and long-term olfactory habituation. While long-term habituation requires activation of CREB, short-term habituation is CREB-independent [44]. Targeting cAMP-PKA may thus have the potential to correct both short- and long-term habituation deficits. Promoting cAMP-PKA activity by pharmacological inhibition of phosphodiesterases (PDEs - negative regulators of cAMP), has shown promising results in correcting cognitive impairment in animal models of neurodevelopmental and neurodegenerative disorders, as well as in patients [216]). PDE3 and PDE4 inhibitors have been shown to improve habituation in wild-type and NF1-deficient zebrafish models, respectively. Two clinical trials with the PDE4 inhibitor Roflumilast in older individuals and patients with schizophrenia showed improvement in verbal memory but not other aspects [188, 189]. In addition, PDE5 (Sildenafil) and PDE9 (PF-04447943) inhibitors are drugs of interest that may improve habituation learning. Sildenafil is approved for treatment of erectile dysfunction and hypertension, but studies in mice suggested that it also has beneficial effects on learning and memory [203]. PF-04447943 demonstrated to improve performance in a rodent attention task [202]. The drug did not show an effect in clinical trials for Alzheimer Disease, but has not been evaluated for other disorders.

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4.3.2. Synaptic plasticity and excitability

Synaptic plasticity is considered a major neuronal mechanism of habituation. It is therefore not surprising that products of many genes with evidence for habituation deficit from multiple species act in synaptic plasticity, in addition (and using) the signaling pathways highlighted above. They control presynaptic neurotransmitter release (dysbindin encoded by *DNTBP1* [217]), synaptic vesicle recycling (*AP2S1* [218]) (**Figure 4B**) and postsynaptic receptor function (NMDA Receptor subunits encoded by *GRIN1*, *GRIN2A* and *GRIN2B*; α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor encoded by *GRIA1*; Dopamine receptor D1 encoded by *DRD1*; Acetylcholine muscarinic receptor encoded by *CHRM2*) (**Figure 4A**). Interestingly, NMDA receptor antagonist Memantine was reported to successfully restore impaired habituation in patients with fragile X-associated tremor/ataxia syndrome, as measured with EEG in an auditory oddball paradigm [219]. Memantine was also tested in three phase 2 clinical trials in ASD cohorts. In the first lead-in open-label trial, 517 (59.6%) individuals responded with improved Social Responsive Scale (SRS). While the following double-blind withdrawal trial found no difference in loss of treatment response between continued Memantine treatment and placebo, an open-label extension trial revealed further SRS improvement with extended Memantine treatment, which may be of clinical importance [220]. A recent small double-blind trial with focus on neurocognitive measures found beneficial effect of Memantine on verbal recognition memory and verbal intelligence quotient (VIQ). The authors further hypothesize that Memantine's effect more likely originates from cognitive enhancement than reduction of behavioral problems [221].

Disruption of several genes encoding the voltage-gated calcium ion (Ca^{2+}) channels (zebrafish *cacna1c* (human *CACNA1C)* and *cacnb2a/b* (*CACNB2)*, *Drosophila Ca-alpha1T (CACNA1G/H/I)*, *C. Elegans unc-2* (*CACNA1A/B/E)* and *unc-36* (*CACNA2D1-4)*) result in impaired habituation learning. These channels play a key-role in neuronal signal propagation, including through signal transduction cascades depicted in **Figure 4A**. Mutations in these genes

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cause ID and ASD syndromes, and aberrant function has been associated with various psychiatric disorders (reviewed in [222]). Two Ca^{2+} channel inhibitors, Verapamil and Nimodipine, are FDA-approved for hypertension and cognitive protection after subarachnoid hemorraghe, respectively. Interestingly, both drugs showed also positive effect on habituation learning in wild-type zebrafish in the already mentioned compound screen [182], suggesting a substantial role of Ca^{2+} channels in habituation learning.

It is worth to highlight the emerging importance of intrinsic excitability (IE) that in synergy with synaptic plasticity shapes synaptic strength, synchronic neuronal activity and engram formation. A role for IE in habituation is substantiated by numerous voltage-, calcium-, or hyperpolarization-gated potassium (K+) channels in the gene catalog, incl. *KCNA1*, *KCNMA1*, *KCNQ*, *HCN1*, *KCNU1* as well as by further proteins that affect excitability by modulation of K+ channels (*CNTNAP2* [223]) or neurotransmitter release (*PRKG1* [224]). Disruption of *KCNMA1* results in habituation learning deficits in *Drosophila*, mouse, and rat and is associated with autistic traits in humans [225]. This gene encodes a subunit of big calcium-gated K+ channels (BK-channels) that locate close to the glutamatergic pre-synapse and are essential for synaptic depression, one of the underlying mechanisms of habituation. Local administration of BK-channel activator Flindokalner in the region where auditory afferent synapses project on sensorimotor neurons enhanced habituation of the acoustic startle response in rats[190]. BK-channels are widely expressed and the drugs currently available exert too many side effects to be safely administered in humans. Ezogabine and Lamotrigine, however, are K+ channel targeting drugs that are FDA-approved for epilepsy, Lamotrigine also for bipolar disorder. Interestingly, Lamotrigine was found to improve associative learning deficits in a mouse model of NF1, as its target *HCN1* channel interacts with neurofibromin [206] and a clinical trial to assess cognitive improvement in patients with Neurofibromatosis 1 is ongoing (NCT02256124).

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4.3.3. Translational control

Fragile X syndrome (FXS), the most frequent ID and ASD syndrome, is caused by transcriptional silencing of the *FMR1* gene. It has been extensively studied and habituation deficits have been reported in animal models of multiple species and in FXS patients [66]. The encoded fragile X mental retardation protein (FMRP) is a synaptic activity-dependent repressor of translation with a critical role in synaptic plasticity [226]. Preclinical studies in animal models improved the understanding of FXS biology and provided promising drug targets. However, numerous FXS clinical trials failed to meet the primary endpoints that were usually based on questionnaires and caretaker reports [227]. However, here we would like to highlight a small, double-blind, placebo-controlled crossover treatment trial that incorporated electrocortical activity measures as a sensitive, objective method for monitoring treatment responses. This trial showed that three months of treatment with Minocycline restored abnormal habituation of event-related potentials (ERPs) in an auditory oddball task in a group of children with FXS [69]. As an antibiotic, Minocycline is thought to exert those beneficial effects through repression of neuroinflammation. However, its habituation-improving action has been linked to inhibition of matrixmetalloprotease-9 (MMP-9), a target of FMRP-mediated translational inhibition that is upregulated in the auditory cortex of Fmr1 KO mice [228]. MMPs are proteases that are involved in activity-dependent organization of the extracellular matrix [229]. In line with this, mechanosensory habituation to taps was impaired in two zebrafish models with loss-of-function mutations in *mmp16a* and *mmp16b*, orthologues of human *MMP-16* [135]. Adjunctive treatment with Minocycline to the antipsychotic Risperidone in 46 children with ASD showed positive effects on irritability and hyperactivity scores, but not for lethargy/social withdrawal, stereotypic behavior, and inappropriate speech scores [230], once more highlighting the need for cognitive or cognition-relevant outcome measures.

Beyond translational control, also aspects of mRNA processing are crucial to habituation, as identified by two further ‘multispecies hit’ genes. *UPF3A/B* (orthologues to

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Drosophila Upf3 and *C. Elegans smg-4*) is involved in nonsense-mediated mRNA decay and human variants have been associated with neurodevelopmental disorders including ASD [231]. GIGYF1/2 (orthologues to zebrafish gigyf2, *Drosophila CG11148*, and *C. Elegans C18H9.3*) regulates decay of transcripts mostly associated with secretory, membrane-bound, and actin-related processes [232], but also of *DUSP6*, a negative regulator of *ERK* (Ras-MAPK signaling) [233]. Variants in *GIGYF1/2* have been associated with both neurodegenerative and neurodevelopmental disorders in animal models and human cohorts [234, 235].

5. Clinical relevance, applications and assessment of habituation learning

Having extracted genes and molecular pathways involved in habituation, and highlighted targets for intervention, we in this section summerize the spectrum of disorders and clinical phenotypes that have been associated with habituation deficits. We point to disease symptoms that that may be a direct consequence of habituation deficits and highlight further evidence linking habituation to cognitive functions. We also provide an overview of various methods to assess habituations in human research, with a focus on those that have been applied in monogenic neurodevelopmental disorders.

5.1. Habituation deficits in disease

Habituation deficits have been reported in multiple cognitive disorders, including neurodevelopmental, -psychiatric and -degenerative disorders [8]. Our inventory of genes and molecular pathways implicated in habituation, mostly through animal work, illustrates that the overlap with disease genes causally implicated in monogenic neurodevelopmental syndromes is large (see **Figure 4A-C** and SysID database [179] at www.sysid.dbmr.unibe.ch), instantly supporting a correlation between habituation and higher cognitive functioning. It should be noted though that we and others have intentionally investigated disease genes and hence the high degree of overlap is not unbiased. Yet, mutations in disease gene orthologs have also been

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identified to cause habituation deficits in unbiased approaches (e.g., *PDE4E, CAMTA1, CNTNAP2, CASK, PC, OGT*). Unfortunately, human habituation data to complement the animal studies are lacking for the vast majority of these monogenic neurodevelopmental syndromes. Assessing habituation in these individuals is challenging, because these syndromes are rare (posing a logistic challenge) and often come with moderate to severe cognitive impairment, interfering with the ability of individuals to partake in standard habituation paradigms. Low-burden, passive protocols and special expertise are required, examples of which are discussed below in section 5.3. Using such procedures, habituation deficits have been reported in patients with co-occurring ID and ASD [236], most importantly in Fragile X syndrome, the most common monogenic cause of ID and ASD [62-65, 67, 237-239]. The requirement of the human Fragile X protein FMRP for habituation is matched by extensive preclinical evidence from mouse [96, 240], *Drosophila* [141, 241], and zebrafish [137], providing first support for conserved mechanisms and the translational value of multiple habituation measures across species. Whereas Fragile X syndrome for two decades remained the only syndrome in which habituation was investigated, recently others have followed ([72] and several ongoing). Clearly, expanding assessment of habituation in monogenic neurodevelopmental syndromes could greatly contribute to consolidate and further unravel the genetic landscape of habituation. At the same time, these disorders could tremendously profit from habituation as an objective outcome measure, e.g. in clinical trials.

Compared to monogenic neurodevelopmental syndromes, habituation is much better explored in ASD. In ASD cohorts, impairments in habituation have been found throughout development (e.g.[55, 242-244]. Reduced habituation has been observed as early as 3 or 6 months of age in infants at familial risk for ASD [245, 246]. In children diagnosed with ASD of age 7 to 13 years, habituation deficits have been shown to correlate with several clinical scores associated with competence along diverse phenotypic dimensions, such as a social communication score and parents' questionnaire scoring the severity of sensory difficulties

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[244]. Reduced habituation is also widely observed in adults diagnosed with ASD (e.g. [247, 248]). Habituation deficits are thought to contribute to some of the core symptoms of ASD, such as learning difficulties, social deficits and sensory hypersensitivities, caused by defective filtering and resulting information overload [249]. A functional study into hypersensitivity has shown that ASD individuals with high sensory overresponsitivity showed reduced ability to maintain habituation in the amygdala and relevant sensory cortices and to maintain inhibition of irrelevant sensory cortices [55], providing empirical support for the "intense world" theory of ASD, and fitting with the network plasticity model of habituation [43].

Habituation abnormalities have also been observed in several other neurodevelopmental disorders, including Attention-deficit/hyperactivity disorder (ADHD), schizophrenia, Obsessive Compulsive Disorder (OCD), and Tourette Syndrome (TS). In ADHD, impaired habituation has been reported in both children [250] and adults [251]. However, other studies reported enhanced habituation associated with the disorder [252-254].

A larger body of studies has reported habituation deficits in Schizophrenia (e.g. [255-257]) reported reduced hippocampal habituation in schizophrenic patients to correlate with memory performance for word pairs, and suggested that reduced habituation may contribute to the memory deficits commonly observed in schizophrenia. In OCD, habituation has recently emerged as a potential mechanism underlying sensory symptoms of OCD [258-260]. Benito, Machan [258] used independent observers to continuously rate fear changes during exposure-based Cognitive Behavioral Therapy (CBT), and determined habituation by summing decreased fear that could not be explained by an observable exposure event (i.e. that could not be explained by a change in the exposure stimulus, safety signals, distractors, rituals, etc., but rather occurred "on its own", thereby signaling therapeutic learning). They found that patients with OCD and greater habituation showed larger reductions in symptom severity, greater global improvement, and increased odds of treatment response.

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Also in patients diagnosed with TS, impaired habituation has been described [261, 262] and was hypothesized to contribute to sensory feelings that give rise to the urge frequently preceding a tic [263].

Another disorder for which numerous electrophysiological studies have described hyperresponsivity to repeated sensory stimuli and impaired habituation is migraine [9]. Habituation is usually assessed in the periods between migraine attacks (i.e. the interictal phase) in episodic migraine patients. In these periods, reduced to complete loss of habituation is reported [264-266]. Children with migraine with the most defective habituation have been shown to have the worst behavioral symptomatology (as assessed by the Child Behaviour Checklist, CBCL) [265].

Abnormal habituation has also been observed in the neurodegenerative movement disorders Huntington's and Parkinson's diseases (HD, PD). In contrast to the habituation deficit phenotype that is most often observed in the previously discussed disorders, studies in HD mostly report enhanced habituation [267-270]). The most commonly used paradigm in HD patients is habituation of the blink reflex in response to taps on the forehead (sometimes referred to as habituation of the Glabella Tap Reflex) or in response to electrical stimulation. The enhanced habituation phenotype in HD has been suggested to underlie the associated motor abnormalities (i.e. chorea), as supported by the positive correlation between habituation and the severity and distribution of the facial chorea [271]. Although there is some support for the idea that enhanced habituation in HD reflects over-inhibition of dopaminergic receptors in the striatum [268], it may be necessary to exclude that enhanced habituation cannot be attributed to muscle fatigue. We found no clinical follow-up studies on habituation ability in HD patients from the past two decades. The most recent studies of habituation in HD, in mouse models, have provided seemingly conflicting results. Two studies reported habituation deficits, in habituation to novel environment and open field habituation respectively [133, 134], whereas another reported enhanced open field habituation in an HD mouse model [272]. Also in this

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mouse study, muscle fatigue has not been excluded to cause the reduction in exploratory activity. In PD patients, habituation deficits are well-established and have been used as a diagnostic tool for decades, with habituation of the Glabella Tap Reflex as the most common paradigm for assessment [273-275]. The habituation impairments in PD patients have been shown to positively correlate with the years since PD diagnosis [10] and severity of motor symptoms [276-278].

These findings of abnormal habituation patterns in HD and PD are contrasted by the absence of habituation deficits in another common neurodegenerative disease; in patients diagnosed with Alzheimer's Disease (AD), there have been numerous reports showing preserved habituation despite severe associative learning and memory deficits [279-282]. The clear absence of habituation deficits in AD demonstrates that habituation deficits are not merely a side effect of any type of neurological dysfunction.

5.2. Habituation and Cognition

In addition to the relevance of habituation for a variety of neuronal disorders, there is a large body of evidence showing the importance of habituation abilities for neurotypically developing individuals. As already indicated in the introduction, habituation has been proposed to be a building block for higher forms of cognition [12, 283-285]. It is the earliest form of learning to develop, with habituation responses to an auditory stimulus occuring in fetuses as young as gestational age of 22 weeks [286], and many studies reported habituation in older fetuses [287-292]. Since the earliest measurement of a habituation response to an auditory stimulus coincides with the onset of fetal auditory abilities [293], other forms of habituation might already be present before this gestational age [294]. Gonzalez-Gonzalez, Suarez [292] showed that fetal habituation rate correlates to neonatal habituation rate at 1-2 days after birth. Moreover, several longitudinal studies have shown that the rate of infant habituation is one of the best predictors of an individual's later IQ [1-7, 295]. Together, these findings suggest that habituation performance is a strongly genetically determined nervous system property, and that

554 an individual's habituation ability relative to the habituation ability of others is maintained over
555 time.

556 In young healthy adults, a recent study on acoustic startle habituation assessed the
557 relation between habituation and resiliency to adverse and potentially traumatic events. Walker
558 et al. found that fast habituating individuals showed lower depression/anxiety and higher
559 resilience [296]. The authors concluded that their habituation paradigm can be used to overcome
560 the self-reporting bias in commonly-used psychometric approaches and provide a method for
561 objective assessment and monitoring of psychological resilience. These studies further
562 highlight the relevance of habituation in cognitive performance and quality of life, two
563 parameters that further increase the relevance of habituation as a clinical outcome measure for
564 various diseases.

565 In addition to the large amount of clinical and scientific literature supporting habituation
566 as a disease- and cognition-relevant property, there are also reports that did not find significant
567 anomalies in habituation in individuals diagnosed with the aforementioned disorders (e.g. in
568 OCD [297-299], ADHD [300-303], schizophrenia [304], and HD [305, 306]), or found no
569 correlation between habituation and measures of IQ [244]. We noticed that most of these studies
570 used an experimental design that was not optimized to assess habituation, but e.g. derived
571 measures of habituation from other protocols, e.g. assessing pre-pulse inhibition (PPI).

572 ### 5.3. Habituation tests in neuroscience and the clinic

573 A multitude of different paradigms, varying in stimulus and type of readout, are used to
574 assess habituation in human (clinical) research. Usually, the stimuli are repeated a certain
575 amount of times with a constant inter-stimulus interval and consist of one sensory modality.
576 These stimuli range from simple visual, olfactory, or auditory (startle) stimuli, such as light
577 flashes, stationary objects or simple tones, to more complex stimuli like (emotional) faces and
578 speech. There are studies showing large correlations between habituation ability to different
579 sensory modalities within individuals. Miller et al. for example, measuring habituation of

electrodermal responses (EDRs) in individuals with FXS for five modalities of sensory stimulation in an electrodermal activity (EDA) habituation paradigm, found that the pattern of EDRs to stimulation in one sensory modality predicted the pattern of EDRs in the other four [63]. A recent study by Côté et al. employed a multisensory stimulus to assess habituation of EEG patterns during an audio-visual task in four ID syndromes (i.e. FXS, tuberous sclerosis complex (TSC), Down syndrome (DS), or ID due to SYNGAP1 mutations) [236]. They reported intact habituation in individuals with FXS and DS, which they propose might be due to an increased sensitivity towards the multi-sensory stimulus compared to stimuli of a single sensory modality. More work is required to get a comprehensive picture of the impact of the type of stimuli, and this may even depend on the investigated disorder.

Besides the wide variety of utilized stimuli, human (clinical) habituation studies employ(ed) paradigms with a multitude of different readouts to assess habituation. Commonly used behavioral and physiological habituation paradigms in human and animal studies are listed in **Table 1**, section 3.3. In addition, some studies have assessed habituation by patient self-report or family-report through questionnaires [259, 307, 308]. These self-reported measures of habituation were shown to partially correlate to physiological habituation measurements in an EDA habituation paradigm in individuals with OCD [259].

Taken together, to tap the full potential of habituation as a translational readout to better understand cognition in health and disease, fundamental questions such as the impact of the utilized paradigm (i.e. stimuli and readout) onto phenotypes remain to be investigated further.

6. Conclusions

In this review, we have identified 258 evolutionary conserved genes that have been demonstrated in the primary literature to underlie habituation in one or several species. Our species-specific gene catalog shows that most of the genes have been identified in animal models, particularly in invertebrates amenable to testing behavioural phenotypes on a larger

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scale. The so far small number of genes unambiguously linked to habituation deficits in humans reflects that in contrast to cognitive neuroscientists, clinical researchers investigating cohorts with specific monogenic neurodevelopmental syndromes have developed interest in habituation rather recently. Even though assessment of habituation in these cohorts requires dedicated protocols, expertise and logistic efforts to collect data from these rare disease cohorts, such efforts are extremely worthwhile as they open unique opportunities into translational neuroscience and clinical care. Our survey demonstrates that many of the identified genes and pathways show overlap between different species and various types of habituation. They also strongly overlap with genes implicated in other forms of learning, memory, ASD and related neurodevelopmental syndromes. Based on this functional conservation and relevance to disease mechanisms, we propose that habituation can serve as a superior functional readout to overcome a number of challenges that the field of neurodevelopmental disorders is facing:

On the preclinical side, research in animal models can identify mechanisms and thereby treatment targets that underlie habituation deficits. Candidate repurposeable drugs, some of which highlighted in this review, can be experimentally tested for their potential to alleviate deficits in habituation as a predictive proxy for cognition; some animal models and habituation paradigms even are suitable for unbiased drug screening. Furtheron, testing novel candidate genes and variants of unknown significance identified in the clinic for habituation deficits in animal models can help to establish causality and contribute to diagnostics.

On the clinical side, habituation as a highly cognition-relevant readout may provide an outcome measure that is meaningful to daily life quality of patients and can be objectively/quantitatively measured, of high value to assess treatment efficacy in clinical trails.

Lastly, habituation measures, collected either preclinically (for cohorts with genetic data and identified likely gene disrupting mutations) or in the clinic, may proof a useful stratification tool to improve design and success of clinical trials. High heterogeneity of

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underlying defects, e.g. in autism cohorts, can mask treatment effects if only beneficial for subsets of patients.

We conclude that habituation has already been studied intensively in animal disease models, and that its application in the clinic is currently gearing up. Together, preclinical and clinical habituation may be able to provide the much needed, well-aligned translational pipeleine that can overcome current bottlenecks in research, diagnostics, preclinical drug discovery, clincal assessment of disease state and treatment efficacy, and even provide novel means for stratification.

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