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Genetics, molecular control and clinical relevance of habituation learning.

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Abstract

Habituation is the most ancient and fundamental form of learning. As a firewall that protects our brain from sensory overload, it is indispensable for higher cognitive processes. Studies in humans and animal models provide a growing body of evidence that habituation is affected in autism and related monogenic neurodevelopmental disorders (NDDs). An integrated application of habituation assessment in NDDs and their animal models has currently unexploited potential for fundamental neuroscience and medical care.

With the aim to gain mechanistic insights, we systematically retrieved genes that have been demonstrated in the literature to underlie habituation. We identified 258 evolutionarily conserved genes across species, describe the biological processes they converge on, and highlight regulatory pathways and drugs that may alleviate the habituation deficits associated with their dysregulation. We also summarize current habituation paradigms and extract the most decisive arguments from the literature that support the crucial role of habituation for cognition in health and disease. We conclude that habituation is a conserved, quantitative, cognition- and disease-relevant process that can connect preclinical and clinical work, and hence is a powerful tool to advance research, diagnostics,'' and treatment of NDDs.

Keywords: Habituation, Genelist, Molecular pathway, Cognition, Neurodevelopmental disorders

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1. An introduction to 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 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, manifesting already before birth [1-6]. Its properties make it a prerequisite to acquire higher cognitive functions [7-12]. In agreement with its fundamental role in cognition, infant habituation levels have been found to predict later IQ better than standardized measures [7-9, 13-16], and deficits in habituation have been linked to several cognitive disorders [17-19]. Habituation is defined by a set of 10 characteristics which, in addition to the response decrement to repeated presentation of the same stimulus (habituation), include: spontaneous recovery, recovery of the response when the stimulus is changed (stimulus specificity), and recovery when a novel stimulus is inserted in the series of habituating stimuli (dishabituation) [10, 20]. A wide range of paradigms is available and used to measure habituation in pre-clinical and clinical settings. While these paradigms differ in the type of the presented stimulus and the measured response, the defining characteristics of habituation are thought to be shared between the various models and paradigms. The most commonly used habituation paradigms in humans and other organisms are described in **Text box 1,** and further discussed in section 4.3.

The strong evolutionary conservation of habituation learning allows researchers to use animal models to dissect its genetic and neuronal mechanisms and study habituation deficits that are associated with human disease. Such insight from animal models may help elucidate disease mechanisms, identify which individuals are more likely to have defective habituation in (genetically) heterogeneous disease cohorts, and stratifying patients for targeted pharmacological treatment strategies. In addition to conventional rodent models such as the mouse (*Mus musculus*) and the rat (*Rattus norvegicus*), research in cost- and time-efficient

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Text box 1: The most commonly used behavioral and physiological methods to assess habituation across organisms. *Since the early stages of habituation research (see **[21]** for a review on the history of the term 'habituation' and habituation research), a range of paradigms have been developed to assess habituation in different organisms, from worms to humans. 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 [22-25]. 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 blinking measured 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. For example, the startle response in rodents is often quantified as the force the animal exerts by the extension of its limbs onto a pressure-sensitive force transducer.

Visual habituation, is also referred to as habituation of looking time, is used in rats and humans [26, 27]. 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 [28], it has been succesfully used to study adults with even profound Intellectual Disability (IQ < 25) [29].

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 [30-34] or, previously, as Galvanic Skin Response (GSR) habituation [35]. 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. As skin conductance reflects the activity of the sympathetic nerve on sweat glands, a decrease in this measure of arousal 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 [36-39]. 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 the habituation of specific brain regions (e.g. amygdala habituation; [40, 41]) in humans and rodents [42]. 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 environment habituation is frequently used in rodent habituation studies and makes use of the natural tendency to explore novelty. A rodent is placed into a novel environment and habituation is determined by total distance traveled or by the amount of time the rodent is actively investigating [43]. It can be assessed within a session or over multiple sessions (i.e. intrasession or intersession habituation) [44]. In habituation studies where a novel 'open field' environment is used, this paradigm is often referred to as open field habituation [45].

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 control of habituation in health and disease. In this review, we first briefly

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summarize habituation theories and mechanisms – neuronal and molecular – that have been uncovered so far and discuss how they contribute to cognitive dysfunction when compromised. Because dozens of studies have reported genes required for habituation learning in the last decades, we moved on to compile them into a systematic catalog. We further analyzed the cellular processes, molecular pathways as well as potential pharmacologic intervention strategies linked to these genes and conditions. We end with a comprehensive overview of the literature that substantiates the importance of habituation in cognition and disease, highlighting habituation to be strikingly relevant to Autism Spectrum Disorder (ASD) and co-occurring neurodevelopmental disorders (NDDs) and discuss the outstanding opportunities that habituation bears to advance research in this field.

2. Habituation theories and mechanisms

The mechanisms underlying neuronal habituation are incompletely understood. Three main theories, originated decades ago, are perceived to be relevant. First, the 'Stimulus-model 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 [46, 47]. Second, the 'Sometimes opponent processes' theory, an adaptation of the former Gnostic unit theory, where the generation of the stimulus-specific neuronal model activates inhibition of an arousal system [48, 49]. Third, the 'Dual-process theory', where interaction between sensitization and habituation in the stimulus-response pathway defines the final response to the stimulus [50]. 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 [51]. According to this model, repeated stimulation modifies the receiver output through time- and stimulus-dependent changes in the habituation element, thereby mediating

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habituation. An equivalent of the 'habituation element' is required in all three described neuronal habituation theories, but its cellular and molecular basis remains abstract.

A few years ago, prior to the definition of this generalizable habituation model, Mani Ramaswami highlighted stimulus-dependent feedback inhibition as a key neuronal mechanism of habituation [52]. He and colleagues experimentally demonstrated that odorant selective habituation in *Drosophila* relies on recurrent inhibitory potentiation of activated excitatory neurons [53-55].

Reviewing seminal electrophysiological studies of the *Aplysia* siphon withdrawal reflex, where homosynaptic depression of excitatory neurons was proposed as the mechanism of short-term habituation [56-58], he noted that even in this model with a simple circuit organization (receptor neurons forming synapses with motor neurons) inhibitory potentiation exists [59, 60]. Inhibitory potentiation can better explain habituation characteristics that are difficult to reconcile with homosynaptic depression, including dishabituation, long-term habituation, and more effective habituation with weak stimuli. The activity of inhibitory neurons also shapes stimulus responses and habituation in the mammalian olfactory bulb [61, 62]. Inhibitory potentiation may thus represent a key mediator of habituation - the 'habituation element' – widely operating across species and paradigms.

As most brain regions consist of connected excitatory neurons that receive inhibitory input, Ramaswami proposed that any repeated excitatory stimulus can, through inhibitory potentiation, create an inhibitory signal (negative image) of itself. This negative image then neutralizes incoming signals of the expected stimulus pattern and strength, thereby acting as a selective filter that suppresses signal transmission to downstream brain regions and/or behavioral responses [52]. An algorithm that implicates the inhibitory potentiation mechanism of habituation is indeed able to efficiently filter out redundant information and detect salient features in the environment [63]. The 'negative-image model' as defined by Ramaswami can thus serve as a general mechanism for adaptive predictive coding.

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Prior experience is encoded in the negative image by scaling of local inhibitory synapse strength. This predicts firing of excitatory postsynaptic target neurons and results in lower responses to familiar stimuli compared to novel, unpredicted ones. An inability to undergo adaptive changes in inhibitory strength weakens encoding of prior experience and impairs predictive abilities. This may underlie sensory hypersensitivities and information overload - key features of ASD [52, 64-66]. The 'negative-image model' further refines the concept of excitation/inhibition (E/I) dysbalance that is commonly considered an etiological mechanism of ASD [67, 68], in the sense that it proposes an inability to undergo adaptive changes rather than steady-state E/I dysbalance, to be the critical factor in ASD-associated cognitive deficits **(Figure 1).**

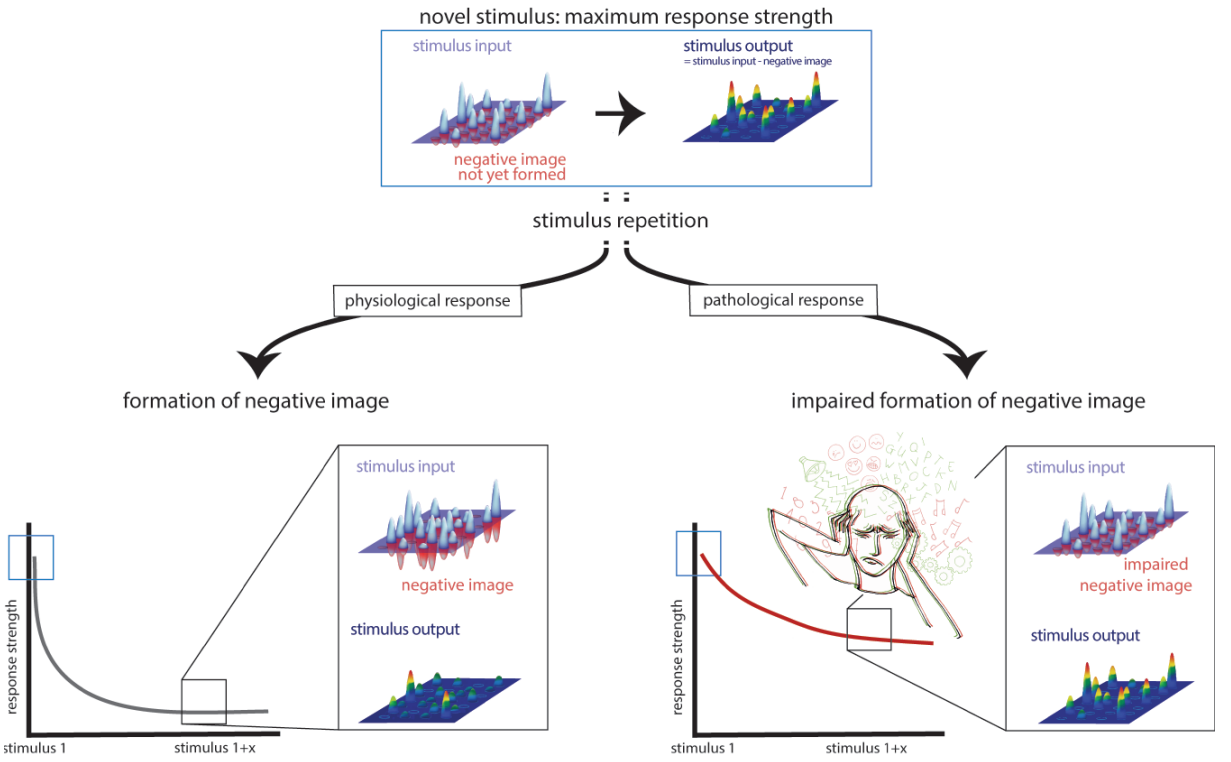

Figure 1. The 'negative-image model' and its relevance to habituation learning and autism. Upon encountering a novel stimulus, the strength of the stimulus output is high because a negative image compensating the stimulus has not been formed yet. In physiological conditions, the repetition of an irrelevant stimulus will lead to inhibitory scaling and formation of a negative image, gradually decreasing the response strength. If in a pathological condition the negative image is not formed (sufficiently), the output and response strength to the repeated stimulus will remain high. The lack of stimulus output attenuation can explain a number of key features of ASD. Part of the figure adapted from M. Ramaswami [52], with permission.

The central molecular mechanism of recurrent inhibitory potentiation revealed by Ramaswami and colleagues is the 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 triggered by Calcium/calmodulin-dependent protein kinase II (CamKII)-dependent phosphorylation of synapsin [54]. However, other kinases that can phosphorylate synapsin (ERK, PKA, CamKI) [69-71] 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 principle excitatory neurons is required to allow for habituation to a specific odor-stimulus [53]. Inhibitory-derived GABA then attenuates the activity of these neurons by binding to GABAA receptors [53]. 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 [53] and probably mediated only by short-term synaptic plasticity mechanisms.

Molecular players and mechanisms required for habituation can further be 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 the years. Still, they have not yet been compiled into a joined framework that contributes to a better understanding of habituation on the molecular level.

3. A comprehensive overview of the molecular basis of habituation

We collected information of all genes, and hence molecular players, that have, to date, been experimentally associated with decreased habituation. We further describe the biological

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processes and molecular pathways that these genes converge on and highlight core pathways that are subject to pharmacological targeting with promising drugs.

3.1. 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 2**. Excluded search terms (indicated by NOT) resulted from earlier searches that exclusively led to studies irrelevant to our aim. The final search string detected 680 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 242 publications, which were viewed in full length. 119 of these provided at least one-to-many unambiguous gene – habituation deficit pairs. Other publications measured habituation 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.

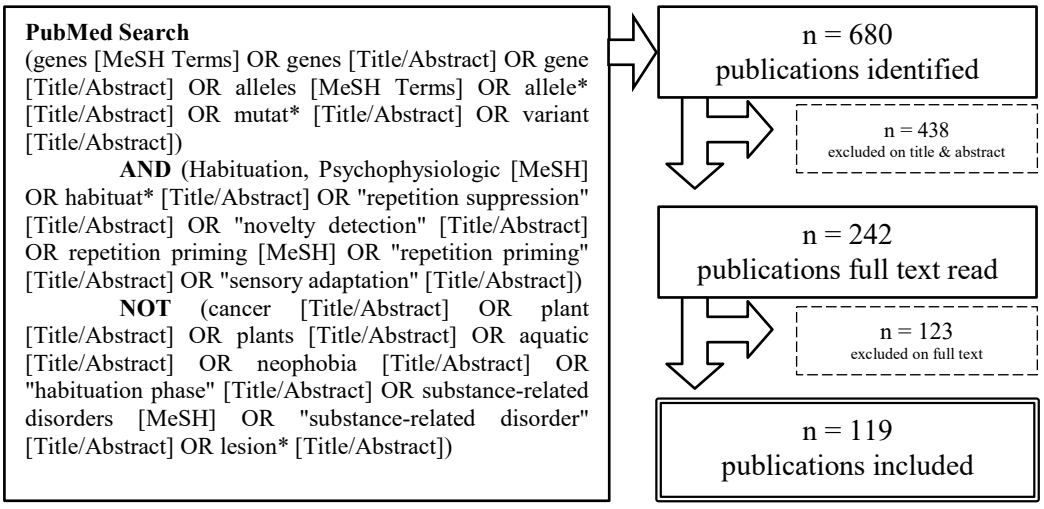

Figure 2. Flow chart depicting the search term and selection process of publications for inclusion into this review.

For the 119 publications, the following aspects were annotated for each monogenic defect found to cause a habituation deficit (**Table S1**): 1. Original gene name in the studied species, 2. Species, 3. Effect on function (LoF, GoF, unknown), 4. Mutation (or manipulation),

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5. Habituation paradigm, 6. Habituation paradigm details, 7. Reference containing PubMed identifier (PMID), year of publication plus name of the first and last author.

In total, our literature review identified 358 hits (either different alleles or the same allele associated with habituation deficits in independent studies) causing reduced habituation learning, in total corresponding to 278 genes in several species (see below), summarized in **Table S1**. Most of the 358 hits induce (predicted) loss-of-function (309 hits). Eighteen 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 [72]. To include top-ranking orthologs and more distal homologs, we applied a number of criteria described in the legend of **Table 1**.

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 insufficiently conserved and excluded from further analyses, leaving us with a catalog of 258 evolutionarily conserved genes to be matched across species (**Table S1**).

The conversion of the model organism gene catalog to human genes inflated the total number of genes from 258 to 421 genes. This can be attributed to one-to-many gene orthologies in *Drosophila* and *C. elegans*, frequently associating a single invertebrate gene to two or several

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human genes forming a related (potentially functionally overlapping or redundant) gene family. To further illustrate the effects of the model organism to human gene conversion, we assigned an inflation score to each organism, calculated as the number of human orthologs divided by the corresponding number of the initially identified genes in the respective species (**Table 1**). 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 1. 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	28	167	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 alphabetical order of the human gene name(s) in **Figure 3**. Genes that have been implicated in habituation in more than one organism are highlighted in dark color and will further be referred to as a multispecies hit. 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 15 additional genes have been found in two species (*AP2S1*, *CNTNAP2, DTNBP1, GRIA1, GRIN1, GRIN2A, KCNA1, KCNMA1, NF1, PC, POGZ, SHANK3, TCF4, TSC1, UPF3A/B*). For 38 additional genes (highlighted in light color), evidence for a role in habituation has been identified either by

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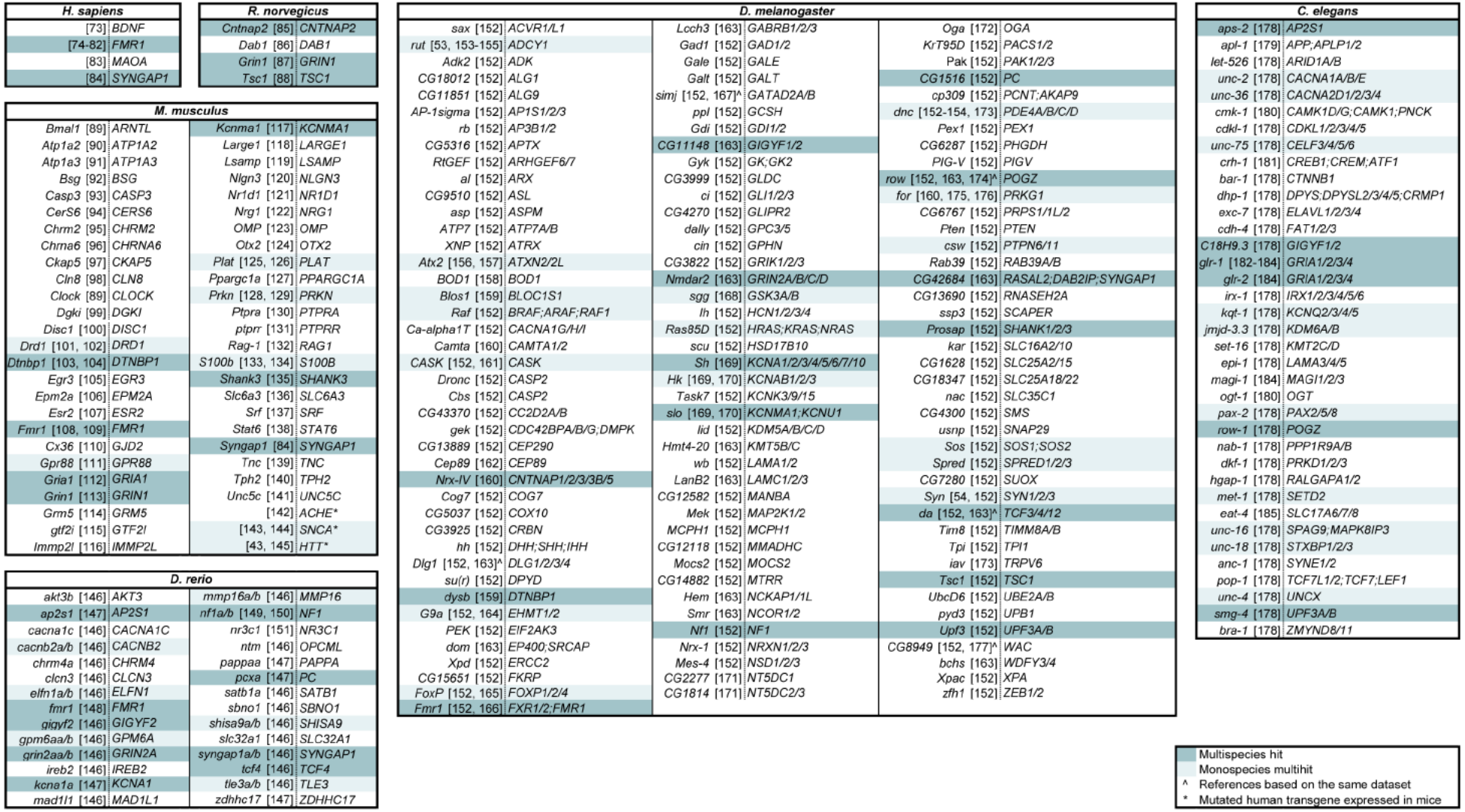

Figure 3: Conserved genes causing reduced habituation upon manipulation. Genes are grouped by the organism in which they were investigated, and alphabetically ordered according to the name of the human ortholog. Depicted is the original gene name with the reference(s), followed by the human gene ortholog(s) 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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multiple independent gene models (hits) by the single indicated reference or in multiple independent studies within the same species. These genes are referred to as a monospecies multi-hit.

The compiled catalog contains genes with diverse protein functions. In the next section, we aimed to identify the biological processes that they function in and focus on druggable signaling pathways that comprise multispecies hit habituation genes.

3.2. Gene ontology

To describe the biological processes in which the catalogued genes function, we subjected them to Gene Ontology (GO) classification via AmiGO2 analysis [186-189] (DOI: 10.5281/zenodo.4495804 Released 2021-02-01). Guided by the fold enrichment and p-values from the AmiGO2 analysis, we identified which GO terms could give a general overview of the biological processes in which a big proportion of the catalogued genes are involved without turning to very big/general or small/specific GO terms. Additionally, we limited the complexity of the GO outcome by manually combining functionally-related identified GO terms into compound GO terms [190]. For example, the compound GO term 'MAPK cascade' is comprised of the GO terms 'regulation of MAPK cascade', 'MAPK cascade', 'regulation of ERK1 and ERK2 cascade', 'negative regulation of MAPK cascade', and 'negative regulation of ERK1 and ERK2 cascade'. We provide a detailed description of the GO terms covered by the compound GO terms in **Table S2**.

Figure 4 depicts 11 compound GO terms that we have identified to be enriched in and describe a large proportion of our gene catalog. Together, they describe the biological functions for 73% of the identified 398 human genes n = 290 human gene orthologs). Genes connected to only one of the 11 compound GO terms are shown on a dark background (n = 152, 53%), while genes connected to more than one of the depicted compound GO terms are shown on a light background (n = 138, 47%). The Venn diagram depicts the six compound GO terms with the most genes associated with only a single described compound GO group, showing that even

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these processes are genetically still very much connected. Five further compound GO terms are depicted separately to limit the complexity of the Venn diagram and because these terms overlap considerably with the genes already present in at least one other compound GO term, and thus add rather few genes only associated with a single compound GO term.

The Venn diagram highlights genes associated with the compound GO terms: regulation of transcription (n = 91 genes | of which 35 associated only with this compound GO term), cation transport (n = 65 | 35), syapse organization & transmission (n = 98 | 29), metabolic process (n = 35 | 27), MAPK cascade (n = 46 | 14), and chromatin organization (n = 43 | 9). The genes operating in the largest number of represented biological functions are *APP* (associated with 7 of 11 compound GO terms), *CTNNB1* (7 of 11), *PTEN* (7 of 11), *DLG1* (6 of 11), *GRIN1* (5 of 11), *KRAS* (5 of 11), *NRXN1* (5 of 11) and PRKN (5 of 11).

It is not surprising that our gene list identifies biological processes related to synapse organization & transmission andlearning or memory; 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. These processes are highly implicated in NDDs [190, 191] and are at least partly 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.

3.3. Molecular pathways, processes, and their drugability

Whereas the GO analysis provided an overview of biological functions prominently involved in habituation, it does not capture all genes and points to very broad processes, except for MAPK and Wnt signaling. Aiming to identify clinical applications, we found it worthwhile to zoom in further and define additional molecular pathways in which genes required for habituation operate. Due to the large number of genes and space constraints we focused on

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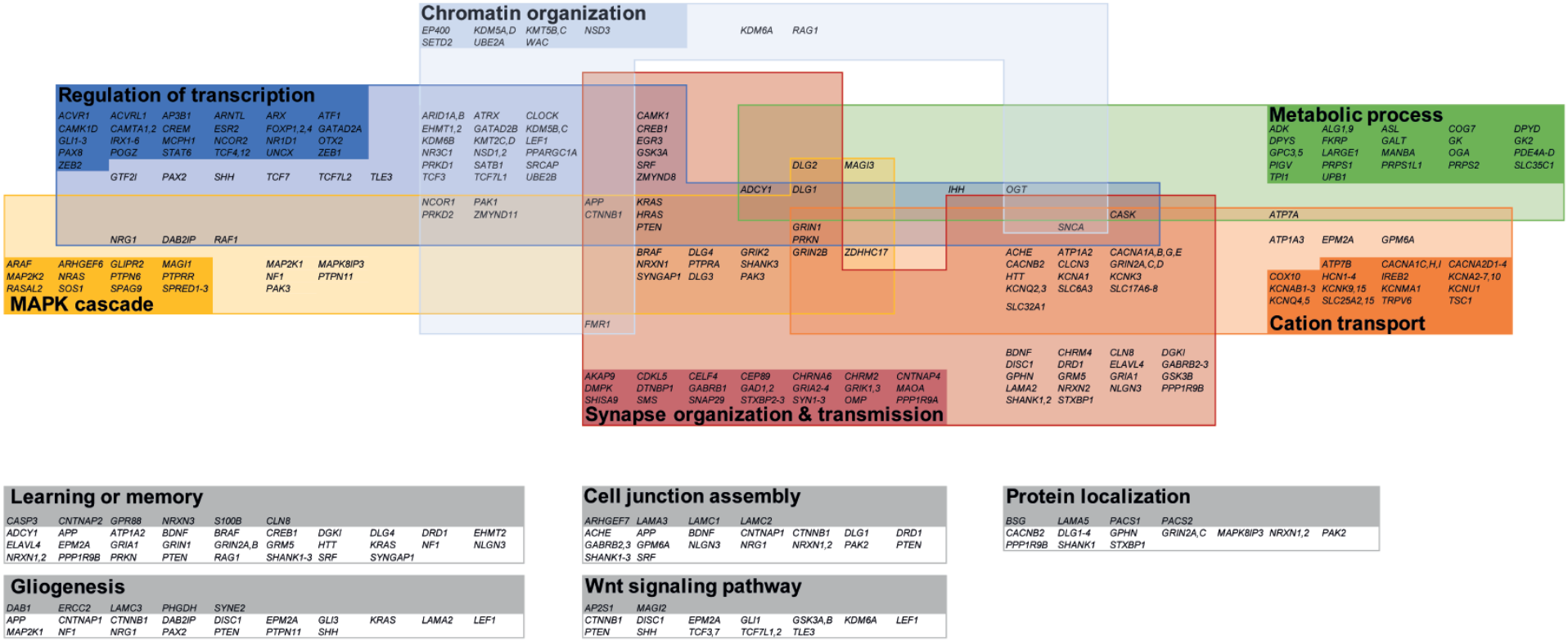

Figure 4: Venn diagram of compound GO terms describing biological processes linked to genes required for habituation. Compound GO terms represent functionally related GO terms (**Table S2**). The Venn diagram connects the 6 compound GO terms that contribute most genes only connected to a single compound GO term (dark background). Genes connected to multiple compound GO terms are shown on a light background.

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depicting those pathways and processes that aggregate a number of multispecies hit genes (in red; 17 of 18) and monospecies multihit genes (in orange; 29 of 38) in **Figure 5**. These include (1) central cellular signal transduction cascades PI3K-AKT-mTOR, Ras-MAPK, and cAMP-PKA (**Figure 5A**), (2) mechanisms of neuronal plasticity and excitability (**Figure 5B**), and (3) the control of protein translation (**Figure 5C**). Because these interconnected processes align well with the major mechanistic themes in NDDs [192], they also are attractive targets for pharmacological intervention.

Habituation learning as well as its genetic and molecular mechanisms appear to be deeply conserved. Small animals thus offer the opportunity to conduct drug testing *in vivo* at reasonable costs on a bigger scale. Such screens may uncover novel lead compounds, which has been impressively demonstrated by a compound screen that assessed the effect of 1760 compounds on acoustic startle habituation in wild-type zebrafish larvae [193]. Nineteen compounds were found to improve habituation learning. Most of these are targeting neurotransmitter systems. Eight of them are targeting disease mechanisms highlighted here, including intracellular signaling molecules (GSK3B, PKC, and PDE3), post-synaptic receptors (DRD and CHRM) and channels (CACNA1C) (**Figure 5**).

Figure 5D provides a synopsis of compounds for which a positive effect on habituation (**Figure 5D**, left column) has been demonstrated, or compounds with hypothetical suitability based on targeting the depicted habituation-relevant pathways and evidence on the beneficial effect of these drugs for cognition (**Figure 5D**, right column). Many of these drugs are repurposable; 11 of them are already approved by the U.S. Food & Drug Administration (FDA). Four additional drugs are currently being investigated in clinical trials. These central habituation pathways and their drugability will be further discussed in the following subsections.

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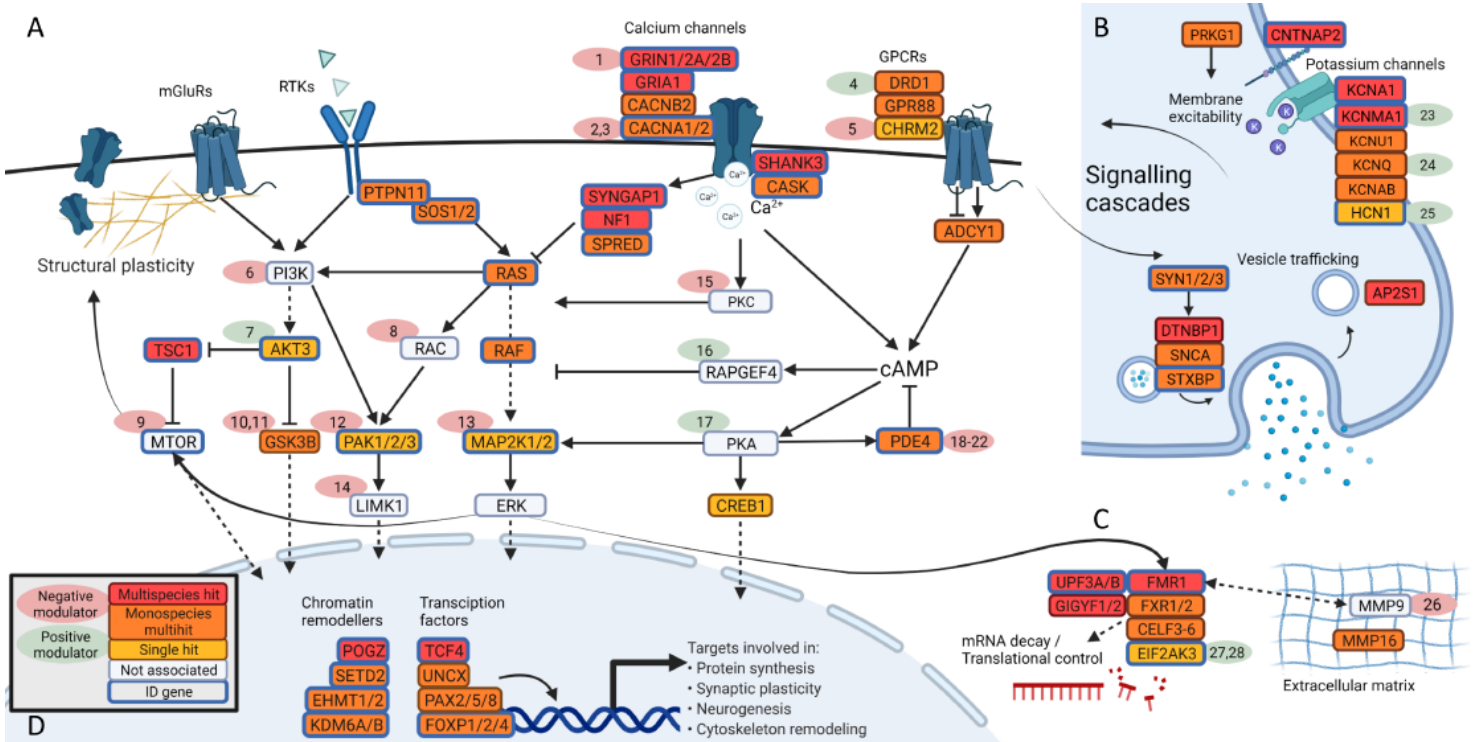

Drugs improving habituation learning

#	Drug	Target	Medical indication	Reference
1	Memantine	GRIN	Alzheimer's dementia*	80
2	Verapamil	CACNA1C	Hypertension*, cluster headache**	193
3	Nimodipine	CACNA1C	Neuroprotective after subarachnoid hemorrhage*	193
4	cis8-OH-PBZI hydrobromide	DRD3	-	193
5	Trihexyphenidyl hydrochloride	CHRM1	Parkinsonism*	193
10	Indirubin-3'-monoxime	GSK3B	Alzheimer's***	193, 194
11	Kenpaullone	GSK3B	ALS***	193, 195
15	Chelerythrine chloride	PKC	Chemo-induced memory deficit***	193, 196
17	8-Br-cAMP	PKA	-	149
18	Olprinone hydrochloride	PDE3	Cerebral oxygen supply during surgery**	193, 197
19	Rolipram	PDE4	Depression**	149, 198
20	Roflumilast	PDE4	COPD*, cognitive impairment**	149, 199, 200
23	Flindokalner	KCNMA1	Fragile X***	201, 202
26	Minocycline	MMP16	Antibiotic*, neurodevelopmental disorders**	81

Drugs hypothetically improving habituation learning

#	Drug	Target	Medical indication	Reference
6	Buparlisib	PI3K	Cancers**	203
7	SC79	AKT	Cancers***, Alzheimer's***	204
8	EHop-016	RAC1	Cancers***, Alzheimer's***	205
9	Everolimus	mTOR	Cancers*, TSC (tumours and seizures)*	206, 207
12	IPA-3	PAK1	Cancers***	208
13	Selumetinib	MEK	NF1 (neurofibromas)*	209, 210
14	SR7826	LIMK	-	211
16	8CPT-2MecAMP	RAPGEF4	-	212
21	PF-04447943	PDE9	Alzheimer's**	213
22	Sildenafil	PDE5	Erectile dysfunction*, hypertension*	214
24	Ezogabine	KCNQ	Partial-onset seizures*, depression**	215, 216
25	Lamotrigine	HCN1	Bipolar disorder*, epilepsy*	217
27	CCT020312	EIF2AK3	-	218
28	Salubrinal	EIF2A	-	219

Figure 5. Schematic overview of the molecular processes and mechanisms comprising most multihits and/or drugable gene products. 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 intellectual disability [190] 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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Intracellular signaling cascades

PI3K-AKT-mTOR and Ras-MAPK signal transduction cascades are key players of cell growth, proliferation, and cancer, but they also have a well-established, crucial role in neuronal development and synaptic plasticity. The cascades cross-talk at multiple levels (**Figure 5A**). Presynaptically, mTOR-dependent protein translation is important for the growth and regeneration of axonal terminals. Postynaptically, activation of mTOR by N-methyl D-aspartate (NMDA) and metabotropic glutamate (mGluR) receptors increases local protein in dendrites, thereby contributing to structural plasticity (reviewed in [220]). Phosphorylation of synapsin by ERK (Ras-MAPK) is required for presynaptic neurotransmitter release and hippocampus-dependent learning in mice [221] (**Figure 5A,B**).

Germline mutations in the key players and the regulators of the depicted cascades cause monogenic neurodevelopmental syndromes characterized by intellectual disability (ID) and, frequently, also ASD [192, 222] (**Figure 5**, genes with blue frames). Moreover, the baseline activity of PI3K-Akt-mTOR and Ras-MAPK is increased in idiopathic ASD cohorts and correlates with clinical severity [223]. In *Drosophila* light-off jump habituation, Ras-MAPK signaling is sensitive to opposing effects depending on the type of neuron in where the pathway was genetically targeted. An increase of Ras-MAPK in inhibitory, GABAergic neurons, as well as a decrease of Ras-MAPK in excitatory, cholinergic neurons, impairs habituation learning [152]. Partial loss of negative Ras-MAPK regulators *SYNGAP1* or *NF1* is associated with habituation deficits in *Drosophila,* mice and zebrafish [84, 146, 149, 150, 152]. Furthermore, *SYNGAP1* mutations were shown to cause habituation deficits in mice and patients, as assessed by translational EEG approaches [84]. *NF1* haploinsufficiency causes Neurofibromatosis type 1 (NF1), a genetic disorder with a 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 [149].

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Furthermore, post-hoc assessment of four combined trials evaluating the MEK inhibitor Selumetinib in treating *NF1*-associated neurofibromas suggests no adverse and beneficial effects on cognitive readouts [210].

cAMP acts as a second messenger in numerous signal transduction pathways. cAMP-activated PKA phosphorylates SNARE regulatory proteins and synapsins, which leads to enhanced synaptic vesicle release and short-term synaptic plasticity [224, 225] (**Figure 5B)**. cAMP-PKA also mediates long-term synaptic plasticity through transcriptional regulation via activation of CREB [226]. In the proposed inhibitory potentiation mechanism of habituation, cAMP is required for both short- and long-term habituation. 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 [227]). PDE3 and PDE4 inhibitors improved 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 [199, 200]. In addition, PDE5 (Sildenafil) and PDE9 (PF-04447943) inhibitors are drugs of interest that may improve habituation learning. Sildenafil is approved for the treatment of erectile dysfunction and hypertension, but studies in mice suggested it also has beneficial effects on learning and memory [214]. PF-04447943 improved performance in a rodent attention task [213]. The drug did not show an effect in clinical trials for Alzheimer's Disease (NCT00930059) but has not been evaluated for other disorders.

Synaptic plasticity and excitability

Synaptic plasticity is considered a major neuronal mechanism of habituation. Therefore, it is not surprising that the protein of many genes with evidence for cross-species habituation

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deficit act in synaptic plasticity. Involved signaling pathways control presynaptic neurotransmitter release (dysbindin encoded by *DNTBP1* [228]), synaptic vesicle recycling (*AP2S1* [229]) (**Figure 5B**) 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 5A**). 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 [230]. 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 an improved Social Responsive Scale (SRS) score. 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 might be of clinical importance [231]. A recent small double-blind trial focusing on neurocognitive measures found a 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 the reduction of behavioral problems [232].

Disruption of several genes encoding subtypes of voltage-gated calcium (Ca^{2+}) channels (zebrafish *cacna1c* (human *CACNA1C) [146]* and *cacnb2a/b* (*CACNB2) [146]*, *Drosophila Ca-alpha1T (CACNA1G/H/I) [152]*, *C. Elegans unc-2* (*CACNA1A/B/E) [178]* and *unc-36* (*CACNA2D1-4)[178]* result in impaired habituation learning. These channels play a key role in neuronal signal propagation through controlling presynaptic vesicle release and activation of the signal transduction cascades depicted in **Figure 5A** [233, 234]. Mutations in these genes cause ID and ASD syndromes, and their dysregulation has been associated with an increased risk for various psychiatric and neurologic disorders [235]. Ca^{2+} channel inhibitors are

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404 successfully used in some of these conditions, such as pain and seizures [235]. Two inhibitors,
405 Verapamil and Nimodipine, are FDA-approved for hypertension and cognitive protection after
406 subarachnoid hemorrhage, respectively. Interestingly, both drugs also showed a positive effect
407 on habituation learning in wild-type zebrafish in the already mentioned compound screen [193],
408 suggesting a substantial role of Ca^{2+} channels in habituation learning.

409 It is worth highlighting the emerging importance of intrinsic excitability (IE) that, in
410 synergy with synaptic plasticity, shapes synaptic strength, synchronic neuronal activity and
411 engram formation. A role for IE in habituation is substantiated by numerous voltage-, calcium-
412 , or hyperpolarization-gated potassium (K+) channels in the gene catalog, incl. *KCNA1*,
413 *KCNMA1*, *KCNQ*, *HCN1*, *KCNU1* and other proteins that affect excitability by modulation of
414 K+ channels (*CNTNAP2* [236]) or neurotransmitter release (*PRKG1* [237]). Disruption of
415 *KCNMA1* results in habituation learning deficits in *Drosophila*, mouse, and rat and is associated
416 with autistic traits in humans [238]. This gene encodes a subunit of big calcium-gated K+
417 channels (BK channels) located close to the glutamatergic pre-synapse and are essential for
418 synaptic depression in habituation. Local administration of BK channel activator Flindokalner
419 in the region where auditory afferent synapses project on sensorimotor neurons enhanced
420 habituation of the acoustic startle response in rats. BK channels are widely expressed, which
421 could lead to the exertion of too many side effects by the currently available drugs making them
422 unsafe to be administered in humans. However, Ezogabine and Lamotrigine are K+ channel
423 targeting drugs that are both FDA-approved for epilepsy, and Lamotrigine is additionally
424 approved for bipolar disorder. Interestingly, Lamotrigine was found to improve associative
425 learning deficits in a mouse model of NF1, as its target *HCN1* channel interacts with
426 neurofibromin [217], and a clinical trial to assess cognitive improvement in patients with
427 Neurofibromatosis 1 is ongoing (NCT02256124).
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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 FXS patients [78]. The encoded fragile X mental retardation protein (FMRP) is a synaptic activity-dependent translation repressor with a critical role in synaptic plasticity [239]. Preclinical studies in animal models improved the understanding of FXS biology and provided promising drug targets. Though, numerous FXS clinical trials failed to meet the primary endpoints that were usually based on questionnaires and caretaker reports [240]. Still, 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 [81] but did not assess behavioral outcome. 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 matrix metalloprotease-9 (MMP-9), a target of FMRP-mediated translational inhibition that is upregulated in the auditory cortex of *Fmr1* KO mice, a model with EEG-defined acoustic habituation defects [241]. MMPs are proteases that are involved in the activity-dependent organization of the extracellular matrix [242]. 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* [146]. Adjunctive treatment with Minocycline to the antipsychotic Risperidone in 46 children with ASD showed positive effects on irritability and hyperactivity scores but not on lethargy/social withdrawal, stereotypic behavior, and inappropriate speech scores [243], but habituation was not assessed. In conclusion, the same drug (Minocyline) showed positive effects on EEG-defined habituation in mouse models and patients with *Fmr1* mutations, and it

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selectively benefited behavioral outcomes in an idiopathic ASD cohort. However, the lack of measuring both habituation and behavioral outcomes within one study does not allow drawing a direct link between restored habituation and improved behavioral outcomes.

Beyond translational control, aspects of mRNA processing are crucial to habituation, as identified by two further 'multispecies hit' genes. *UPF3A/B* (orthologues to *Drosophila Upf3* and *C. Elegans smg-4*) is involved in nonsense-mediated mRNA decay, and human variants have been associated with NDDs, including ASD [244]. *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 [245], but also regulates decay of *DUSP6*, a negative regulator of *ERK* (Ras-MAPK signaling) [246]. Variants in *GIGYF1/2* have been associated with both neurodegenerative and NDDs in animal models and human cohorts [247, 248].

Taken together, we show that most genes with evidence from multiple species highlight (pharmacologically targetable) processes that are compatible with a key role of synaptic transmission. The rest of all identified genes provide equally exciting starting points for refining the neuronal mechanisms of habituation. Moreover, understanding which of these genes cooperate and how could serve as a basis to target specific groups of genetically heterogeneous patients with standard treatment.

4. 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 summarize the spectrum of disorders and clinical phenotypes that have been associated with habituation deficits. We highlight evidence linking habituation to cognitive functions and point to disease symptoms that may be a direct

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consequence of habituation deficits. We also discuss various methods to assess habituations in human research, focusing on those applied in monogenic NDDs.

4.1. Habituation and cognition

A large body of evidence shows the importance of habituation for cognitive function. As already indicated in the introduction, habituation has been proposed to be a building block for higher forms of cognition [10, 249-251]. It is the earliest form of learning to develop, with habituation responses to an auditory stimulus occurring in fetuses as young as the gestational age of 22 weeks [1], and many studies reported habituation in older fetuses [3-6, 252, 253]. Since the earliest measurement of a habituation response to an auditory stimulus coincides with the onset of fetal auditory abilities [254], other forms of habituation might already be present before this gestational age [255]. Gonzalez-Gonzalez, Suarez [253] 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 [7-9, 13-16, 256]. In addition, a recent study in infants found electrophysiological correlates of habituation to be associated with adaptive skills and structural and functional brain changes associated with age, demonstrating habituation's predictive value for neurodevelopment[257]. Together, these findings suggest that habituation performance is a strongly genetically determined nervous system property and that an individual's habituation ability relative to the habituation ability of others is maintained over time.

A recent study on acoustic startle habituation in young, healthy adults assessed the relation between habituation and resiliency to adverse and potentially traumatic events. Walker, Thomson [258] found that fast habituating individuals showed lower depression/anxiety and higher resilience. The authors concluded that their habituation paradigm can be used to overcome the self-reporting bias in commonly-used psychometric approaches and provide a method for objective assessment and monitoring of psychological resilience.

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These studies highlight the relevance of habituation in cognitive performance and quality of life, two parameters that endorse habituation as a clinical outcome measure for various diseases.

4.2. Habituation deficits in disease

Habituation deficits have been reported in multiple cognitive disorders, including neuro-developmental, -psychiatric and -degenerative disorders [17]. 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 5A-C** and SysID database [190] at www.sysid.dbmr.unibe.ch), 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 degree of overlap is not unbiased. Yet, mutations in disease gene orthologs have also been identified to cause habituation deficits in unbiased approaches (e.g., *CAMTA1 [160], CASK [152, 161], CNTNAP2 [85, 160], OGT [180] , PC [147, 152], PDE4A-D [152-154, 173], SYN1 [54, 152]*). Unfortunately, human habituation data to complement animal studies are still lacking for the vast majority of monogenic neurodevelopmental syndromes. Assessing habituation in those individuals is challenging, because these syndromes are rare; posing a logistic challenge. Moreover, monogenic neurodevelopmental syndroms often come with moderate to severe cognitive impairment, interfering with the ability of individuals to partake in habituation paradigms that can be applied to neurotypical individuals. Low-burden, passive protocols and expertise are required, examples of which are discussed below in section 4.3. Using such procedures, habituation deficits have been reported in patients with co-occurring ID and ASD [259], most importantly in FXS, the most common monogenic cause of ID and ASD [74-77, 79, 260-262]. The requirement of the Fragile X protein FMRP for habituation in humans is matched by extensive preclinical evidence from mice [108, 263], fruit flies [152, 264], and zebrafish [148], providing first support for conserved mechanisms and the translational value

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of multiple habituation measures across species. Furthermore, for two decades, Fragile X syndrome remained the only syndrome in which habituation had been investigated. However, recent efforts are gearing up and habituation has started to be assessed in cohorts with mutations in *SYNGAP1* [84], *NF1* (ongoing; personal communication Sarah Lippé, University of Montreal), *CHD8*, *GRIN2B*, *SCN2A*, and *DYRK1A* (ongoing; personal communication Caitlin M. Hudac, University of South Carolina). Clearly, expanding the assessment of habituation in monogenic neurodevelopmental syndromes could greatly contribute to consolidating and further unraveling the genetic landscape of habituation. At the same time, these disorders could tremendously profit from habituation as an objective outcome measure for neurocognitive profiling and 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.[64, 265-267]). Reduced habituation has been observed as early as three or six months of age in infants at familial risk for ASD [268, 269]. 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 [267]. Reduced habituation is also widely observed in adults diagnosed with ASD (e.g. [270, 271]). Hypersensitivities, a common feature of ASD, are connected with impairments in predictive ability. Both may arise from defective habituation (explained in section 'Habituation theories and mechanisms'). Accodingly, in a fMRI study, ASD individuals with sensory over-responsitivity exhibited reduced ability to maintain habituation in relevant sensory cortices and downstream brain regions [64]. Because of this, as postulated in a unifying theory of autism neurobiology, 'the intense world theory', individuals with ASD may percieve the world too intense, less predictable, and adopt strategies that minimize contact and interaction with the outside world [272]. However, during brain development, especially in early childhood,

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external input is necessary and lack of it may result in social and language impairments [273]. Other fMRI studies measuring amygdala habituation to images of faces and houses showed impairments in ASD adults specifically to faces, and correlating with the level of social dysfunction [274, 275]. Together the findings of these studies can explain how habituation deficits can contribute to a broad range of ASD symptoms, beyond sensory hypersensitivities, such as learning difficulties, language and social deficits.

Habituation abnormalities have also been observed in several other NDDs, 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 [276] and adults [277]. However, other studies reported enhanced habituation associated with the disorder [278-280].

A larger body of studies has reported habituation deficits in schizophrenia (e.g. [281-283]). Williams et al. [282] 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 the sensory symptoms of OCD [284-286]. Benito, Machan [284] 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 (e.g. due to avoidance), 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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582 Also in patients diagnosed with TS, impaired habituation has been described [287, 288]
583 and was hypothesized to contribute to sensory feelings that give rise to the urge frequently
584 preceding a tic [289].

585 Another disorder for which numerous electrophysiological studies have described
586 hyperresponsivity to repeated sensory stimuli and impaired habituation is migraine [18].
587 Habituation is usually assessed in the periods between migraine attacks (i.e. the interictal phase)
588 in episodic migraine patients. In these periods, reduced to complete loss of habituation is
589 reported [290-292]. Among children with migraine, those with the most defective habituation
590 had the worst behavioral symptomatology (as assessed by the Child Behaviour Checklist,
591 CBCL) [291].

592 Abnormal habituation has also been observed in the neurodegenerative movement
593 disorders Huntington's and Parkinson's diseases (HD, PD). In contrast to the habituation deficit
594 phenotype that is most often observed in the previously discussed disorders, studies in HD
595 mostly report enhanced habituation [293-296]). The most commonly used paradigm in HD
596 patients is habituation of the blink reflex in response to taps on the forehead (sometimes referred
597 to as habituation of the Glabella Tap Reflex) or in response to electrical stimulation. The
598 enhanced habituation phenotype in HD has been suggested to underlie the associated motor
599 abnormalities (i.e. chorea), as supported by the positive correlation between habituation and the
600 severity and distribution of the facial chorea [297]. Although there is some support for the idea
601 that enhanced habituation in HD reflects over-inhibition of dopaminergic receptors in the
602 striatum [294], it may be necessary to exclude that enhanced habituation cannot be attributed
603 to muscle fatigue. We found no clinical follow-up studies on habituation ability in HD patients
604 from the past two decades. The most recent studies of habituation in HD, in mouse models,
605 have provided seemingly conflicting results. Two studies reported habituation deficits in novel
606 environment and open field habituation (respectively [43, 145]), whereas another reported
607 enhanced open field habituation in an HD mouse model [298]. Also in this mouse study, muscle

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fatigue has not been excluded to cause the reduction in exploratory activity. In PD patients, habituation deficits are well-established. They have been used as a diagnostic tool for decades, with habituation of the Glabella Tap Reflex as the most common paradigm for assessment [299-301]. The habituation impairments in PD patients have been shown to positively correlate with the years since PD diagnosis [19] and severity of motor symptoms [302-304].

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 [305-308]. The evident absence of habituation deficits in AD demonstrates that habituation deficits are not merely a side effect of any neurological dysfunction.

In addition to the large amount of clinical and scientific literature supporting habituation as a disease- and cognition-relevant property, there are also reports of intact habituation in individuals diagnosed with the aforementioned disorders (e.g. in OCD [309-311], ADHD [312-315], schizophrenia [316], and HD [317, 318]), or reports that found no correlation between habituation and measures of IQ [267]. We noticed that most of these studies used an experimental design that was not optimized to assess habituation, but derived measures of habituation from other protocols, e.g. pre-pulse inhibition (PPI).

4.3. Habituation tests in neuroscience and the clinic

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

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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 [75]. A recent study by Côté et al. employed a multi-sensory 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) [259]. They reported intact habituation in individuals with FXS and DS, which they propose might be due to 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 potential impact may even depend on the investigated disorder.

Besides the wide variety of utilized stimuli, human (clinical) habituation studies employ 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 **Text box 1**. These paradigms vary in their level of complexity and the physical burden imposed on the participants. Assessing habituation remains challenging in individuals with NDDs, since their ability to partake in the to be conducted tasks may be hampered by limited cognitive abilities and the co-occurence of sensory or motoric difficulties. However, multiple habituation paradigms requiring little-to-no participation from individuals are proven to be suitable for this group. Basic assessment using three-dimensional objects to score habituation of looking time (i.e. visual habituation) has been successful in individuals with an IQ as low as 20-25 [29]. In addition, more recent research has shown that habituation can also be assessed in individuals with severe ID using visual or auditory stimuli and a more complex EEG readout [38, 76, 82]. While this requires additional efforts to maximize the tolerability of EEG caps, the collected data can provide more detailed insights into altered brain responses.

In addition to behavioral and physiological habituation readouts, some studies have assessed habituation by patient self-report or family-report through questionnaires [285, 319,

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320]. These self-reported measures of habituation were shown to partially correlate to physiological habituation measurements in an EDA habituation paradigm in individuals with OCD [285].

Habituation deficits to certain repeating stimuli have been proposed as biomarkers for different disorders (ASD [270], FXS [259, 261], migraine [321]). Although sometimes very specific physiological patterns emerge during habituation assessment [259], a basic phenotyping of habituation ability lacks specificity to distinguish different disorders. We do, however, encourage clinical studies to include careful assessments of habituation. When assessed properly, habituation ability is a valuable addition to many clinical diagnoses. It provides a non-biased physiological and quantitative insight into the basic cognitive functioning of the patient and is thereby a great translational readout for neural dysfunction [322].

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5. Conclusions

In this review, we have identified 258 evolutionarily conserved genes in the primary literature that have been demonstrated 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 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 an interest in habituation rather recently. Even though assessing habituation in affected individuals requires dedicated protocols, expertise and logistic efforts to collect data from 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 NDDs is facing:

On the preclinical side, research in animal models can identify mechanisms and, thereby, treatment targets that underlie habituation deficits. Candidate repurposable drugs, some of which are 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 are even suitable for unbiased drug screening. Further, testing novel candidate genes and variants of unknown significance identified in the clinic for habituation deficits in animal models can help establish genetic causality and contribute to diagnostics.

In the clinic, habituation as a highly cognition-relevant readout may provide an outcome measure that is meaningful to the daily quality of life of NDD patients and can be measured

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quantitatively and objectively. This is of high value to characterize the cognitive profiles of the disorders and assess treatment efficacy in clinical trials.

Lastly, habituation measures, collected either preclinically (for cohorts with genetic data and identified likely gene disrupting mutations) or in the clinic, may prove a useful stratification tool to improve the design and success of clinical trials. High heterogeneity of the underlying defects, e.g. in autism cohorts, can mask treatment effects if they are only beneficial for subsets of patients.

To unlock the full potential of habituation learning as translational bridge for harmonized preclinical and clinical studies in NDDs, future work should aim to refine our understanding of molecular and circuit mechanisms underlying habituation, and determine their specificity versus universality. For this we need comprehensive preclinical and clinical data linking genetic causes of NDDs to habituation deficits, and to determine which habituation paradigms and measures best reflect which disease symptoms and cognitive features.

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