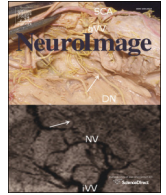




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Cross-species approaches to cognitive neuroplasticity research

J. Mishra^{a,b,*}, A. Gazzaley^{a,b,c,*}

^a Department of Neurology, University of California, San Francisco, San Francisco, CA, USA

^b Department of Psychiatry, University of California, San Francisco, San Francisco, CA, USA

^c Department of Physiology, University of California, San Francisco, San Francisco, CA, USA

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ABSTRACT

Neuroplasticity studies investigate the neural mechanisms that support learning-induced changes in cognition and behavior. These studies are performed in both experimental animals and humans across development from childhood to aging. Here, we review select recent studies that have sought to combine both animal and human neuroplasticity research within the same study. In investigating the same cognitive/behavioral functions in parallel in animals and humans, these studies take advantage of complementary neuroscience research methods that have been established for each species. In animals, these methods include investigations of genetic and molecular biomarker expression and micro-scale electrophysiology in single neurons *in vivo* or in brain slices. In humans, these studies assess macro-scale neural network dynamics using neuroimaging methods including EEG (electroencephalography) and functional and structural MRI (magnetic resonance imaging). Thus, by combining these diverse and complementary methodologies cross-species studies have the unique ability to bridge molecular, systems and cognitive neuroscience research. Additionally, they serve a vital role in translational neuroscience, providing a direct bridge between animal models and human neuropsychiatric disorders. Comprehensive cross-species understanding of neural mechanisms at multiple scales of resolution and how these neural dynamics relate to behavioral outcomes, then serve to inform development and optimization of treatment strategies.

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Introduction

How do cross-species studies enrich neuroplasticity research, inform translational neuroscience and contribute to the development of novel interventions? In this review, we attempt to answer these questions by highlighting select recent studies that have performed cross-species experiments within the same study (Soliman et al., 2010; Pattwell et al., 2012; Sagi et al., 2012; Malter Cohen et al., 2013; Narayanan et al., 2013; Mishra et al., 2014). For each of these studies we describe: (1) the rationale for the cross-species investigation, (2) the experiments performed in animals and humans, and (3) how these experiments provide complementary insight into the cognitive/behavioral phenomenon under investigation. In performing cross-species research, these studies are able to unite a diverse array of genetic, molecular, systems and cognitive neuroscience methods—invasive in animals and non-invasive in humans, and direct them at a specific neuroscientific question. Additionally, we discuss how the study

outcomes contribute to translational research, especially toward the design and optimization of novel interventions. Next generation neurotherapeutics will be powered by the rich diversity of individual information ranging from the genetic scale to the dynamics of macro-scale neural network interactions; cross-species studies are providing these insights in terms of how to integrate diverse neurobiological information and thereby inform personalized interventions that are tailored to the biological state of the developing brain, by genotype as well as cognitive/behavioral phenotype (Lee et al., 2014; Casey et al., 2015). Indeed, such personalized interventions promise greater efficacy, which is aligned with the goals of precision medicine and N-of-1 trial investigations (Schork, 2015).

The studies that we review here span various aspects of learning from fear-conditioning (Soliman et al., 2010; Pattwell et al., 2012) and responding in a novel, threatening environment (Malter Cohen et al., 2013) to spatial learning (Sagi et al., 2012), learning control of motor errors (Narayanan et al., 2013), and maintaining cognitive performance in the presence of sensory distractions (Mishra et al., 2014). Interestingly, while they may appear disparate, what many of these studies have in common is the interaction between the frontal cortex, which enables pro-active top-down control of information processing, and more bottom-up sensory-motor and emotion processing brain regions. For instance, fear conditioning (Soliman et al., 2010; Pattwell et al., 2012) and responding in a novel, potentially threatening, environment (Malter

* Corresponding authors at: University of California, San Francisco-Mission Bay, Sandler Neurosciences Center Room 502 and 511C, MC 0444 675 Nelson Rising Lane, San Francisco, CA 94158.

E-mail addresses: [jyoti.mishra@ucsf.edu](mailto: jyoti.mishra@ucsf.edu) (J. Mishra), [adam.gazzaley@ucsf.edu](mailto: adam.gazzaley@ucsf.edu) (A. Gazzaley).

Cohen et al., 2013) invoke interactions between the prefrontal-amygdalar networks. Prediction error-driven learning involves interaction between medial frontal cortex and motor cortex (Narayanan et al., 2013). And learning to suppress sensory distractions involves prefrontal-sensory cortical dynamics (Mishra et al., 2014). Cross-species investigations in these different learning domains are enabled by the preservation and homology of neural network function across rodents and humans (Buzsáki et al., 2013). Additionally, neurotrophic factors, especially the brain derived neurotrophic factor (BDNF) plays a key role in modulating synaptic plasticity in these networks (reviewed in Rattiner et al., 2005; Casey et al., 2015). BDNF promotes neuronal survival and differentiation, and mediates long-term potentiation especially in the hippocampus, which facilitates learning and memory consolidation. Thus, genetic variation in BDNF expression is of interest to many of these cross-species studies. Overall, common findings across animals and humans confirm the translatability of animal experiment results toward understanding the human brain. Here, we provide an overview of these recent cross-species studies with a common emphasis in each on the rationale for cross-species research, the experimental methods and species-convergent outcomes.

Cross-species understanding of fear learning

Learning to respond to dangerous threats in our environment is an evolutionary necessity. In fear conditioning, an initially non-fear-inducing cue is predictably associated with a threat until the individual learns the cue–threat association and starts to physiologically respond to the cue as if it were itself threatening. Rodents demonstrate a freezing response to the conditioning cue and humans show a pronounced stress response as measured by elevated galvanic skin conductance responses (SCR). The learned fear responses can also be extinguished by repeatedly presenting the cue dissociated from the threat. This is referred to as fear extinction and is the foundation for exposure therapy used in the treatment of anxiety disorders, phobias and post-traumatic stress disorder. Exposure therapy is needed in these neuropsychiatric conditions, as fear extinction is abnormal, i.e. individuals continue to have an abnormal aversive response to neutral cues.

Soliman et al. (2010) applied a cross-species approach to investigate the role of the BDNF gene in fear extinction. The BDNF gene is susceptible to a common mutation at codon 66 where valine (Val) gets substituted for methionine (Met). The Val/Val genotype is thus the typical form of BDNF, while the Met allele (Val/Met and Met/Met) is associated with treatment resistant anxiety-like behaviors (Chen et al., 2006). The rationale for the Soliman et al. (2010) study was to test if BDNF Met allele carriers indeed show differences in fear extinction from non-carriers, in both mice and humans. If this were shown to be the case then there would be compelling evidence for a genetic mouse model for anxiety disorders and a standard fear extinction paradigm could be used to test novel targeted anxiolytic therapeutics developed in mice or humans. The study indeed showed that both mice and human who were Met allele carriers showed impaired fear-extinction. Wildtype mice and typical humans progressively reduced their fear response over early vs. late extinction trials, as measured by percent time freezing in mice and SCR in humans, but Met allele carriers did not (Fig. 1A, B). The authors additionally performed a functional MRI (fMRI) study in humans and showed enhanced activity in ventromedial prefrontal cortex (vmPFC) and reduced responses in the amygdala during extinction in typical humans. Met carriers showed opposing results, i.e. significantly reduced vmPFC activation and significantly elevated amygdala activity (Fig. 1C, D). Thus, Met carriers had altered fronto-amygdalar circuitry. Many studies show that vmPFC signals inhibit the amygdala and thus regulate fear responses (reviewed in Milad and Quirk, 2012). So in the absence of vmPFC activation, Met allele carriers continue to have heightened fear responses supported by the elevated amygdalar activity. The fMRI findings thus extend the validity of the cross-species translation beyond behavior to

neurophysiological mechanisms. Interestingly, since then, these findings have directly informed human clinical research. Zhang et al. (2014) showed that the BDNF Met allele frequency is 2–3 fold higher in US war veterans who met criteria for probable-PTSD (post-traumatic stress disorder) relative to controls. Additionally, Felmingham et al. (2013) showed that patients with PTSD, who carry the BDNF Met allele, have poorer response to exposure therapy than non-carriers.

Pattwell et al. (2012) extended the cross-species research of Soliman et al. (2010) to investigate variations during development, specifically adolescence—an important period in development when extinction is attenuated relative to children and adults. This study, thus, focused on developmental variations but not genetic variations in fear extinction. The authors first demonstrate parallel behaviors in mice and humans, i.e. reduced fear extinction during adolescence, and then perform detailed neurophysiology in mice, specifically in brain slices of the vmPFC regions (infralimbic cortex, IL) that regulate the amygdala and are associated with the suppression of conditioned-fear responses. In this case, parallel cross-species behavior findings provided the rationale for the in-depth electrophysiological follow-up in animals that is not possible in humans, in an effort to build better biological understanding of human learning of fear and anxiety.

Probing vmPFC neural circuitry in mice, Pattwell et al. (2012) showed distinct synaptic plasticity patterns during adolescence relative to childhood and adulthood. Specifically, fear extinction during childhood/adulthood was associated with enhanced glutamatergic synaptic transmission in vmPFC pyramidal neurons, evidenced in elevated excitatory postsynaptic currents (EPSCs), increased AMPA vs. NMDA receptor ratios (as AMPA receptors mediate excitatory synaptic transmission) and enhanced *cFos* immunohistochemistry (a marker for neural activity). vmPFC neurons from adolescent mice showed none of these modifications. These results provide mechanistic evidence for why regulation of fear extinction is blunted during adolescence. As the vmPFC circuitry does not efficiently regulate responses in the maturing amygdala, heightened emotional reactivity is typically observed during this developmental stage (also see Kim and Richardson, 2010; McCallum et al., 2010). Interestingly this research has also benefitted clinical research; trends for such developmental-age specific differences were found in an efficacy analysis of cognitive behavioral therapy for anxiety disorders, with adolescents showing a trend for reduced treatment efficacy relative to preadolescents and adults (Drysdale et al., 2014).

Thus, after demonstrating parallel behaviors across species, Soliman et al. (2010) and Pattwell et al. (2012) further investigated neural function underpinnings in humans and animals, respectively. These studies enrich our fundamental understanding of the mechanisms of fear learning and extinction as it varies with genetics and normal development. Putting together the genetic and developmental findings, the investigators further hypothesize that adolescents with the BDNF Met allele may be more vulnerable to developing symptoms of anxiety as teens, in that they show heightened and prolonged patterns of amygdala activity and reduced vmPFC activity in response to emotional cues. These data, thus, inform personalized therapeutics by suggesting earlier and more intensive anxiolytic therapies for genetically predisposed adolescents and adults (Felmingham et al., 2013; Zhang et al., 2014), who have weaker top-down vmPFC–amygdalar regulation.

Finally in this series of studies, Malter Cohen et al. (2013) investigated the role of early life stress (ELS) induced by orphanage rearing on the development of amygdalar responsivity and top-down vmPFC regulation. Behavior in ELS-exposed humans was measured using a response inhibition task, where they were instructed to respond to neutral faces and withhold responding on rare threatening/fearful faces. Similarly, the ELS mouse model was behaviorally assessed by analyzing the approach to milk feed either in a familiar home cage or an odorless, brightly lit, hence threatening, novel cage. Both ELS exposed humans and mice, relative to controls, had longer response latencies to cues when anticipating a potential threat (Fig. 2A, D). This study performed parallel cross-species neurophysiological investigations of amygdalar activity

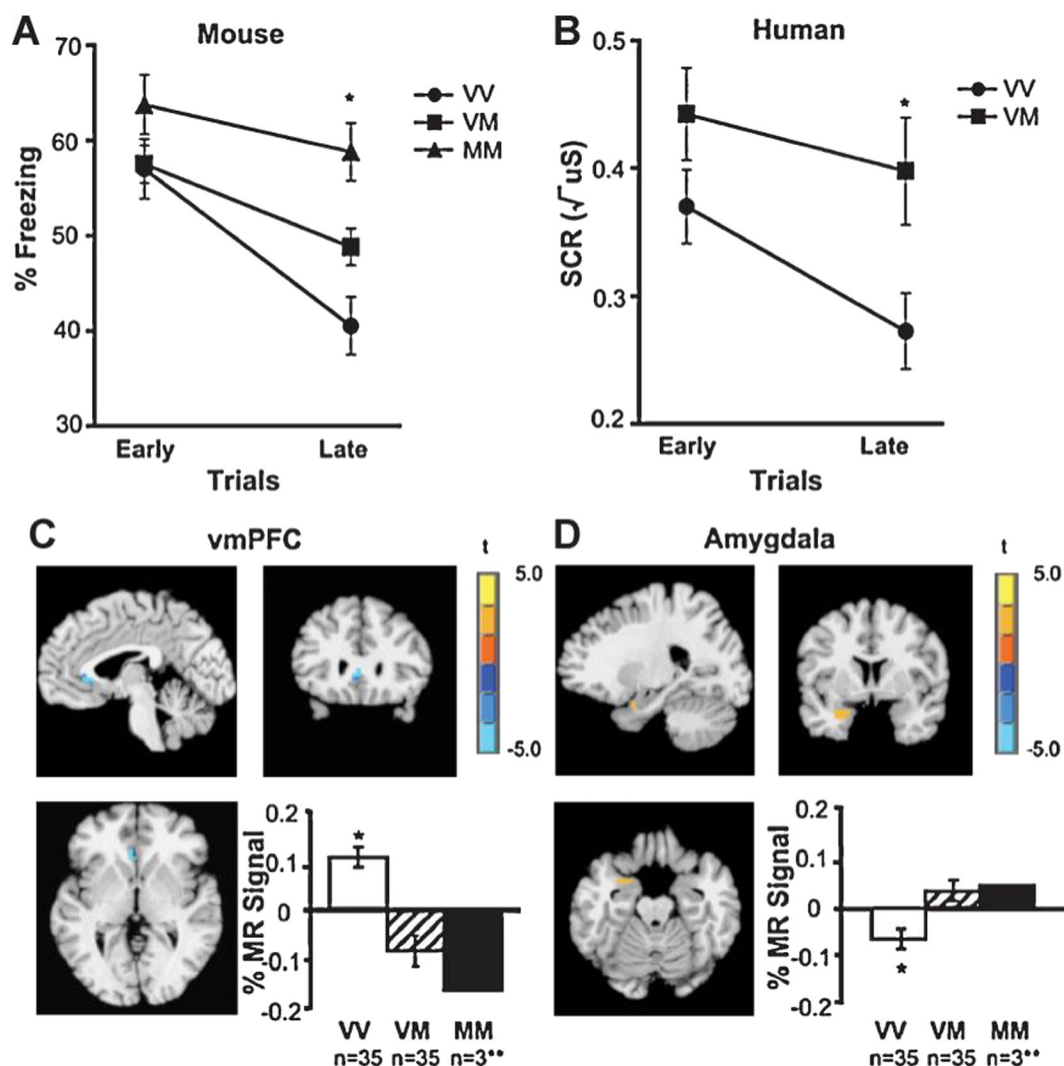


Fig. 1. Altered behavior and neural circuitry underlying extinction in mice and humans with BDNF Val66Met. Impaired extinction in Met allele carriers (Val/Met and Met/Met) as a function of time in 68 mice (A) and 72 humans (B) as indexed by percent time freezing in mice and skin conductance response (SCR) in humans to the conditioned stimulus when it was no longer paired with the aversive stimulus. (C) Brain activity as indexed by percent change in MR signal during extinction in the ventromedial prefrontal cortex (vmPFC) by genotype, with Met allele carriers having significantly less activity than Val/Val homozygotes. (D) Genotypic differences in left amygdala activity during extinction, with Met allele carriers having significantly greater activity than Val/Val homozygotes. All results are presented as a mean \pm SEM. VV = Val/Val; VM = Val/Met; MM = Met/Met. (Adapted with permission from Soliman et al., 2010.)

during the behavioral task, as observed in fMRI BOLD (blood oxygen level dependent) responses in humans and *cFos* immuno-staining (a marker for neural activity) in mice amygdalar slices following threat exposure. Preadolescent ELS exposed individuals in both species showed greater amygdalar responsivity (Fig. 2B, C, E, F). In mice, *cFos* activity in the amygdala as well as in vmPFC slices (in the infralimbic layer) was further probed at preadolescent, adolescent and adult stages. These experiments confirmed significantly heightened amygdalar activity in ELS mice relative to controls, throughout development but most robustly at the preadolescent stage. Additionally, the *cFos* amygdalar activity was paralleled by progressively increasing *cFos* activity in the vmPFC IL layer with development; again suggesting that as vmPFC matures from preadolescence to adulthood, there is better regulation of stress reactivity in the amygdala.

The three studies discussed in this section, thus, elegantly illustrate neuroplasticity in vmPFC–amygdalar networks with differences in genetics (Soliman et al., 2010), stage of development (Pattwell et al., 2012) and ELS environmental exposures (Malter Cohen et al., 2013). In all cases, immature development or reduced neural activity of the vmPFC is present in association with heightened amygdalar activity.

In all cases, the scientists were able to show parallel behaviors and neurophysiology in mouse models and humans, which paves the way for testing novel interventions. With insight into mechanisms, one can hypothesize that neural network targeted interventions that are personalized to the genetic, developmental and life experience of the individual, would be most effective in ameliorating the aberrant responses to cues that signal impending threats. In this regard, there have recently been key breakthroughs in animal research on developing behavioral paradigms that successfully attenuate fear memories (Monfils et al., 2009), which have then been translated to humans (Schiller et al., 2010, 2013). Briefly, fear extinction was shown to permanently attenuate the fear memory only when it was performed shortly after (within 1 h) an isolated fear-associated memory retrieval cue was presented. Xue et al. (2012) further confirmed the potency of this non-pharmacological memory retrieval-extinction procedure, and showed how it can be effectively applied to prevent drug craving and relapse in rat models and abstinent heroin addicts. This elegant series of studies with a primary emphasis on behavioral research are not further elaborated here, but we highly recommend these as further reading.

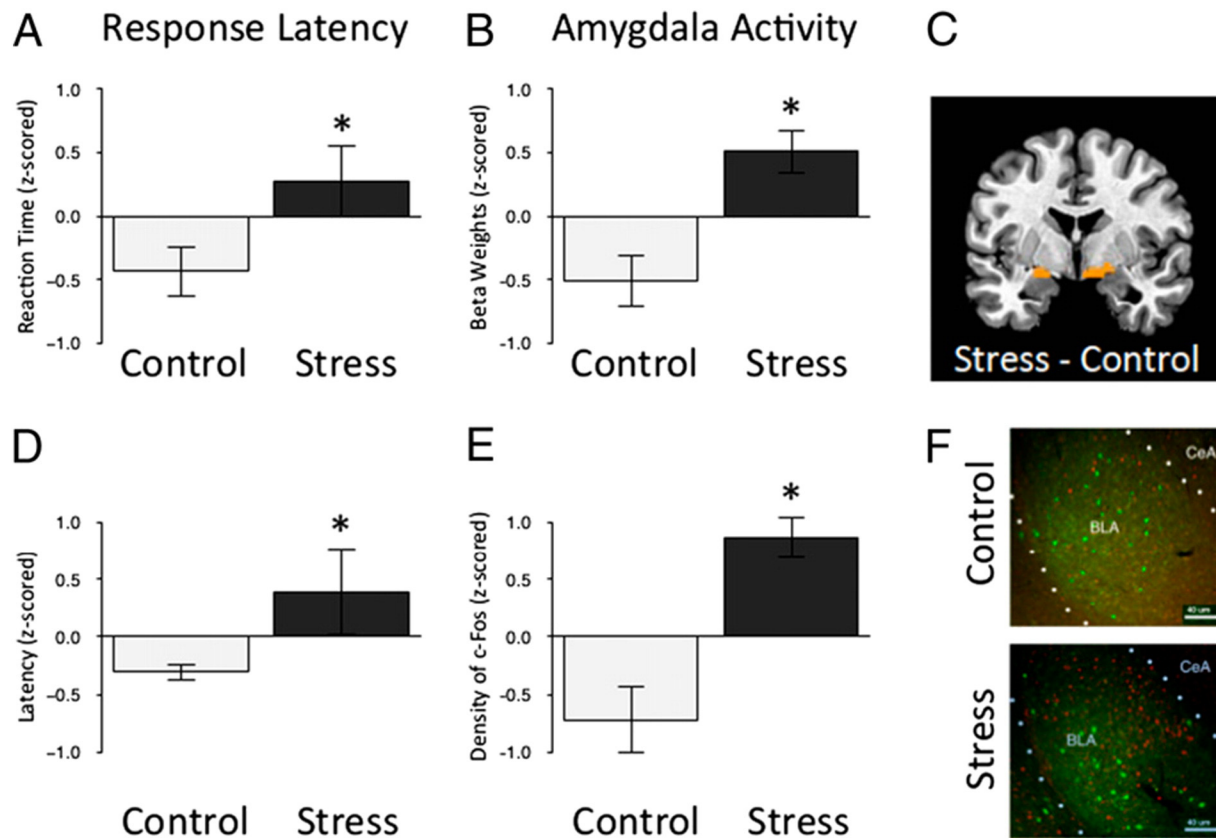


Fig. 2. Greater amygdala activity in humans and mice following ELS (early life stress). (A) Stressed preadolescent humans take longer than their standard reared counterparts to detect frequently presented neutral targets embedded among rare threat nontarget cues that they were instructed to ignore. (B) Parameter estimates of amygdala activity in response to the threat cue (i.e., fearful face) were greater in stressed preadolescent humans than their standard-reared counterparts. (C) Bilateral regions of the amygdala identified as more reactive to threat (i.e., fear face stimuli) in stressed preadolescent humans than their standard reared counterparts. (D) The difference in time that control and stressed preadolescent mice take to approach a cue in a novel cage compared with their home cage. (E) The density of c-Fos protein in the amygdala following exposure to the threatening context (i.e., novel cage) was greater in stressed preadolescent mice than their standard-reared counterparts. (F) An individual slice cut through the amygdala taken from each mouse was stained for c-Fos (red) and PVA (parvalbumin, green) and used for quantification of c-Fos following exposure to the threatening context, clustered by experimental group and at 10 \times magnification. All data are z-scored and expressed as means \pm SEM. (Adapted with permission from Malter Cohen et al., 2013.)

Cross-species plasticity underlying rapid learning

While in the previous section, we described a set of neuroplasticity studies at the prolonged timescales over the course of neurodevelopment, early life experiences and hereditary genetics, here we describe a cross-species neuroplasticity study at the very rapid timescale of two hours. Sagi et al. (2012) tested spatial learning in humans using a car racing video game and asked whether changes in brain structure can be observed after two hours of learning. For this, they employed diffusion tensor imaging (DTI) in humans before and after training, which is sensitive to self-diffusion of water molecules and serves as a marker of tissue architecture. Mean diffusivity (MD) is an outcome measure, which is high if there is ample space between tissue (such as neurons, glia and blood vessels) for water to move freely, but MD is lower if tissue spacing is reduced, possibly driven by growth and proliferation of new neurons, glia or blood vessels (Johansen-Berg et al., 2012). In MD maps generated two hours apart, Sagi et al. (2012) showed significant MD decreases in the hippocampus and parahippocampus—brain regions that are particularly important for spatial learning and memory (Fig. 3A). The study also showed that this structural brain plasticity was behaviorally relevant in that faster learners showed greater decreases in MD. Additionally, an active control group, which also practiced game-based car driving, but without any repetitive learning on a specific spatial track, and a non-training control group did not show these structural changes (Fig. 3B).

To gain a deeper understanding of the rapid structural changes associated with short-term spatial learning, Sagi et al. (2012) performed a

parallel experiment in rats learning a water maze task. So while humans learned the spatial organization of a car-racing track in a video game, rats learned to memorize the location of a hidden platform in a water pool using spatial cues. So even though short-term spatial learning was implemented in both species, apparent differences in task paradigms should also be kept in mind when evaluating the convergence of results between rats and humans.

Like humans, rats showed a decrease in MD in the posterior hippocampus after two hours of spatial learning (Fig. 3C, D). Follow-up immunohistochemistry in the hippocampus of learners vs. controls showed enhanced synaptophysin (a marker of synaptic vesicles), glial fibrillary acidic protein (GFAP; a marker of astrocyte activation and proliferation), and BDNF. These markers suggest that regions of MD decrease may be undergoing rapid structural proliferation of synaptic vesicles and astrocytes with learning. Specifically, activation, proliferation and remodeling of astrocyte and glial processes, which support the cellular learning network, possibly make the most prominent contribution to the MD signal at the rapid hourly learning timescales (Sagi et al., 2012; Johansen-Berg et al., 2012). This is because DTI does not have sufficient resolution to capture changes at the level of synapses resulting from synaptogenesis, and evidence in the literature suggests that neurogenesis and angiogenesis occur on much longer timescales of days to weeks, but not hours.

Overall, the cross-species investigation in this study enabled Sagi et al. (2012) to draw links between microscale cellular dynamics and macroscale measures of structural change. Many open questions remain—how do these structural dynamics evolve with time, are they

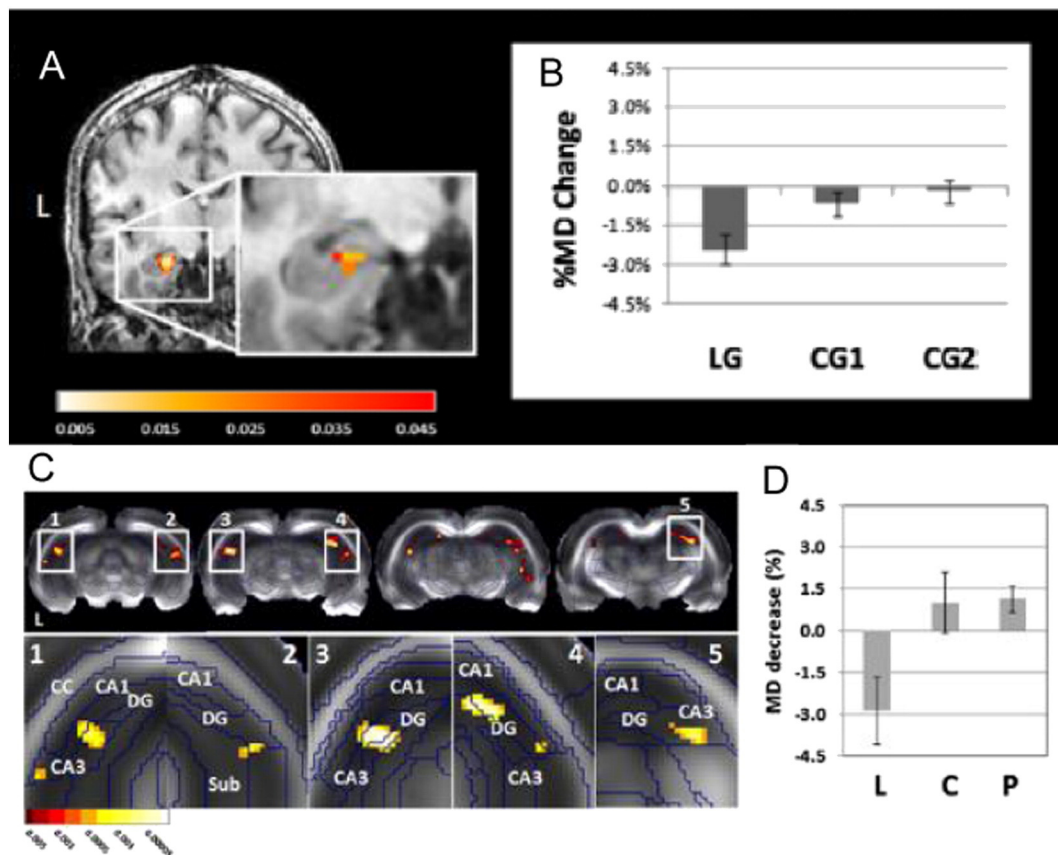


Fig. 3. Structural remodeling of brain tissue measured by DTI as changes in MD (mean diffusivity) after 2 h of training on a spatial learning and memory task. Panels A and B show human data and C and D show rat data. (A) Significant decreases in MD with learning are seen in the human hippocampus and (B) only in the learning group (LG) but not two control groups (CG1 and 2). (C) The posterior hippocampus in rats shows decreases in MD after learning, parallel to findings in humans, and again only in the learning group (L) but not the active control or passive untrained control (C and P). (Adapted with permission from Sagi et al., 2012.)

ephemeral or lead to stable and sustained structural changes, and what learning parameters govern long-term structural stability? Future cross-species studies are needed to comprehensively answer these questions and further our understanding of associations between the micro- and macro-scale neural dynamics.

Cross-species plasticity underlying error-related adaptive learning

Adaptive learning is essential for rapid learning; it allows individuals to appropriately change behavior in response to errors. It is also important to study as it is compromised in several neuropsychiatric conditions (Ridderinkhof et al., 2004; Velligan et al., 2002; Fitzgerald et al., 2005; van Meel et al., 2007), and understanding of its neural mechanisms will lead to better targeted diagnostics and treatments. Narayanan et al. (2013) conducted a cross-species investigation of adaptive learning focusing on the medial frontal cortex (MFC), especially the anterior cingulate, as it has been shown to be involved in adaptive error control in both animals and humans. The authors employed a simple time estimation task in both humans and rats in which a response was required after an estimated time interval (human, 1.4 s; rat, 1 s). EEG and intracortical field potentials were recorded simultaneously with task engagement, at mid-frontal electrodes in humans and medial frontal sites in rodents, respectively. Event related potentials (ERPs) at these sites confirmed conserved processing across species, i.e. enhanced signaling post-error vs. post-correct trials (Fig. 4A, B). Spectral decomposition showed a significant increase in low frequency power (4–8 Hz theta oscillations in humans) exclusively on post-error trials, which was significantly correlated with response latencies (slower responses post-error vs. post-correct trials). These results in humans were paralleled in rats by the intracortical MFC recordings in

the 4–25 Hz frequency range. These data demonstrate that humans and rodents share features of error-driven adaptive control through low-frequency oscillations in the MFC (Fig. 4C, D).

The authors then conducted a detailed electrophysiological investigation of MFC activity and MFC-motor cortex interactions in the rat. Neurophysiological findings were consistent with the role of MFC in behavioral monitoring: (1) Phase coherence of local field potentials (LFP) across MFC and motor cortex sites was enhanced post-error trials. (2) MFC single neuron spikes were coupled to the enhanced low frequency local-field oscillations only on post-error trials. (3) A large fraction of the nearly 100 investigated MFC neurons encoded prior behavioral outcome, while current response latency was encoded by motor cortex neurons. (4) Pharmacological inactivation of MFC eliminated both post-error adaptive control behaviors and underlying neural mechanisms. The inactivated-MFC rats showed greater proportion of errors, shorter response latencies and no post-error slowing. Mechanistically, the selective expression of low-frequency oscillations in motor cortex post-errors, as well as spike-field coherence of motor cortex neurons exclusively post-errors, was eliminated in inactivated-MFC rats.

These results demonstrate the causal role of MFC in adaptive control of action, as well as how it is achieved via selective post-error coupling of motor neuron spike activity to the low frequency oscillations generated by the MFC. The study suggests that individuals with a dysfunctional MFC may function in a mode that is less cognitively flexible and may not benefit from information about previous behavioral outcomes. The conserved neurobehavioral signatures of adaptive control across species further suggest that novel interventions, including targeted neuropharmacology, neurostimulation as well as closed-loop neurofeedback approaches (Mishra and Gazzaley, 2014) that enhance MFC function

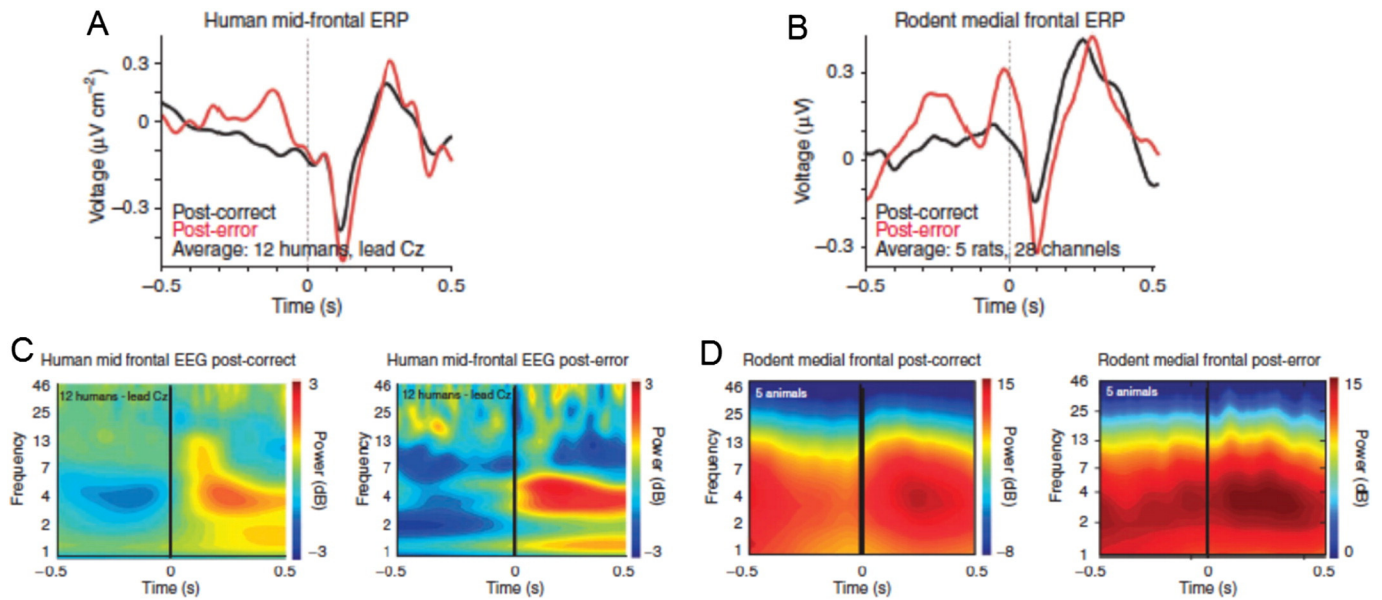


Fig. 4. Common mechanisms of medial frontal cortical oscillations during adaptive control in rats and humans. (A) Average event-related potentials over the midfrontal cortex (electrode Cz) in humans aligned to the target time. Amplitudes were significantly increased in post-error (red) as compared to post-correct (black) trials. (B) Rodent medial frontal field potentials were also significantly increased in post-error (red) as compared to post-correct (black) trials; the results were highly similar to those in humans. (C) Time-frequency analysis revealing enhanced low-frequency power after errors trials relative to correct trial in humans and (D) in rodents. (Adapted with permission from Narayanan et al., 2013.)

can now be tested at multiple levels of neural resolution in animals and humans.

Cross-species validation of behavioral closed loop cognitive training to resolve sensory distractions

We recently conducted a cross-species intervention study to evaluate a targeted and personalized training to ameliorate distractibility in aging (Mishra et al., 2014). The study, conducted in aged rodents and older humans, was motivated by previous demonstrations of a selective deficit in suppressing distractions in both older animals and humans (de Villers-Sidani et al., 2010; Hasher et al., 1999; Gazzaley et al., 2005; Gazzaley, 2013); a deficit that had not been addressed by any other neurotherapeutic approach. In this study, we developed a novel behavioral closed loop distractor training program implemented in the auditory domain. Trainees discriminated specific target tone frequencies from other distracting tones. The training was closed loop and adaptive on each trial, such that correct behavioral performance led to increased distractor challenge (distractor tone frequencies became more similar to the target frequency), while incorrect behavior reduced distractor challenge (distractor tone frequencies became dissimilar to the target frequency). Both older rats and humans performed 36 training sessions, each with a unique set of targets and distractors, over a one-month period. Behavioral and neural outcomes of distractor training were compared to repeated measurements (one-month apart) in untrained control groups. In humans, we also compared results of adaptive distractor training to a mechanistic control, which implemented adaptive target training. The latter training appeared exactly the same as the distractor training with the goal to discriminate targets and distractors; but in this case, training challenge adapted targets (target frequency became more similar to that of distractors on correct responses or became more dissimilar to distractor frequencies on incorrect responses).

In both species, behavioral and neural outcome measures revealed that training resulted in selective improvements in the suppression of distractions; and that these results were specific to the adaptive distractor training intervention and were not observed in control groups. Behaviorally, both trained rats and humans made fewer distractor-related false positive errors (Fig. 5A, B). Neural outcomes

were investigated in the two species using complementary electrophysiological methods—single neuron recordings and auditory tonotopic maps were probed in anesthetized animals and whole-brain EEG was recorded in humans on a target vs. distractor discrimination assessment. Notably, anesthetized recordings in animals allowed us to discern the extent of neuroplasticity in auditory sensory cortex in the absence of top-down regulation, which is not possible in humans.

In rats, single neuron electrophysiology showed selective suppression of distractor processing; in contrast the response to oddball targets was unchanged (Fig. 5C). Tonotopic maps of auditory cortex showed enhanced spatial and spectral resolution of sound frequencies. In humans, early sensory event-related responses to distractors, which localized to auditory cortex, were selectively diminished post-training (Fig. 5D). Similar to findings in rats, responses to targets remained unaltered, and neither of the control groups showed this outcome. This event-related distractor suppression was behaviorally relevant as it correlated to the training gain in sensory resolution. The neural change further correlated with several transfer measures (i.e. assessments of cognitive benefits beyond the trained task), specifically improvements in working memory span and sustained auditory attention. Beyond ERPs, spectral analyses of the human data showed neuroplasticity in frontal low frequency responses (in the theta band). Frontal oscillations localized to the middle frontal cortex near the inferior frontal junction, a region known to play a critical role in interference resolution (Brass et al., 2005; Zanto et al., 2011). Frontal theta was selectively restrained in response to distractors post-training, while the theta response to targets was enhanced. Finally, measures of frontal-sensory theta phase coherence showed selective suppression of this network during post-training distractor processing.

In summary, we found converging evidence in rats and humans that closed loop adaptive distractor training can alleviate deficits in distractor processing. The novel deficit-targeted training procedure was able to harness plasticity at multiple neural scales. (1) At the micro-scale, it achieved selective distractor suppression in single neurons of rat auditory cortex, and thereby improved the signal-to-noise resolution of tonotopic maps. (2) At the macro-scale, it selectively reduced early sensory processing of distractor ERPs in humans. (3) In humans, low frequency oscillations in frontal cortex were also selectively restrained to distractors and frontal-sensory communication

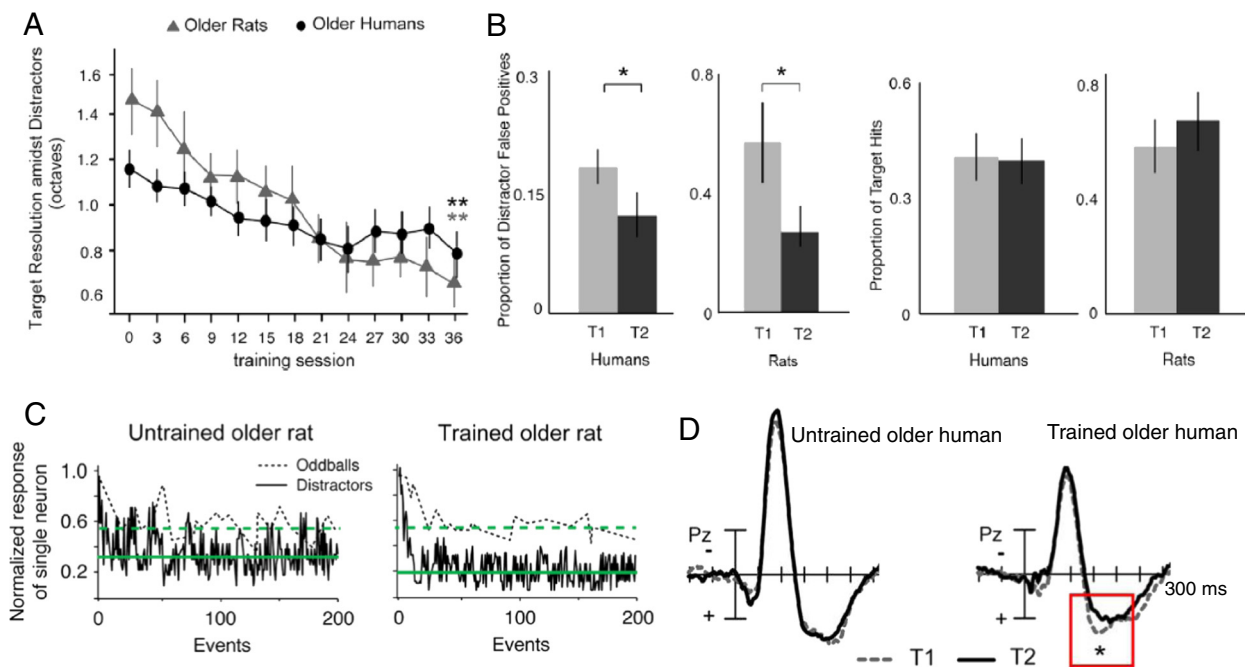


Fig. 5. Evidence for behavioral and neural distractor suppression selectively achieved after adaptive distractor training. (A) Training progressively improved the ability to discriminate target tones amidst varied distractor tones in both rodents and humans (lower octave values imply better discrimination resolution) (B) Underlying the gains in sensory resolution was a selective reduction in false positive errors on distractor trials at the end of training 'T2' assessment relative to baseline, 'T1'. Bar graphs on the right show no significant change in target hits in both species. Data are means \pm SEM. (C) Single neurons in auditory cortex of the trained rat show suppression of distractor processing when a sequence of distractor tones is played to the anesthetized rat ear with infrequent oddball tone stimuli. The green horizontal lines represent the response asymptote of the sample neuron to the oddball and repeating distractor tones; only the response asymptote to the distractors, but not targets, is significantly reduced in the trained rat. (D) ERP recordings to distractor stimuli in humans show a selective reduction in distractor processing at 150–160 ms post-stimulus onset at the T2 vs. T1 assessment, while responses in the control group remain unaltered. Positive microvolt deflections are plotted below the horizontal axis. (Adapted with permission from Mishra et al., 2014.)

(coherence) was suppressed for distractors post-training. Additionally, we showed that this neuroplasticity is directly associated with behavioral gains on-task as well as benefits in untrained transfer measures of sustained attention and working memory span. Overall, our results clearly demonstrated the utility of using a cross-species neuroscientific approach to validate a novel intervention. The study further highlighted how adaptive training mechanics can be specifically focused on a cognitive deficit, heightened distractibility in this case, to generate selective improvements within that neuro-cognitive domain. Notably, these insights inform future closed loop neurotherapeutic research; they provide proof-of-principle that it is possible to engineer closed loop training programs that are selectively targeted to specific behavioral, cognitive and even neural network deficits (Mishra and Gazzaley, 2014).

Discussion

Here, we provide an overview of recent advances in cross-species neuroplasticity research. Each of these studies has significantly contributed toward a deeper scientific understanding of how the brain supports learning. Diverse aspects of learning have been investigated, from negative emotion/fear learning, to spatial learning, to error-related learning, to learning to resolve sensory interference. In performing cross-species research, all of these studies have utilized complementary methodologies in animals and humans within the same study, which converge to provide insights that would be impossible to glean from research in a single species alone. In these studies, expression of parallel behaviors in both species is most commonly the rationale for performing more in-depth neurobiological investigations, using physiological or structural assessment methods appropriate for each species. The mechanistic research integrates findings from genetics, immunohistochemistry and micro-scale electrophysiology in animals with

measures of macro-scale network dynamics probed using EEG/ MRI neuroimaging in humans (Fig. 6).

These cross-species studies substantially contribute to translational research and they generate more credibility for the use of animal models that parallel human behavior (Fig. 6). The detailed neuro-mechanistic knowledge gained from all of these studies has the potential to inform the development of novel interventions, as is already the case for our recent study (Mishra et al., 2014). Of note, the breakthrough studies by Monfils et al. (2009), Schiller et al. (2010, 2013) and Xue et al. (2012) that performed a series of animal and human behavioral experiments across multiple studies to show robust unlearning of fearful memories and addictions, are also very relevant here. Together, these studies inform new interventions, which can now be developed to target an individual's traits such as genetics, life experience and developmental stage as well as their dynamic neural and cognitive states. For instance, the cross-species translational research on fear learning has already directly informed clinical findings of greater risk of PTSD and poor response to exposure therapy in BDNF Met allele carriers (Felmingham et al., 2013; Zhang et al., 2014), and the trend for poor treatment efficacy in adolescents relative to other age groups (Drysdale et al., 2014). Yet, much research still remains to systematically investigate parallels in neuroplasticity across species as a function of age, genetics and life experience.

Mechanistically informed intervention development is extremely important if we are to deliver therapeutics that provide comprehensive and long-lasting benefit to the individual—not just at the level of observable behavior, but also underlying brain function. Furthermore, the task paradigms and assessments in these studies can now be used as biomarkers and outcome measures to evaluate the effectiveness of future intervention research. If an intervention significantly benefits neuro-cognitive status it can be readied for validation in large sample size randomized controlled human trials, which are then followed by studies of practical implementation in the field. In contrast, if the

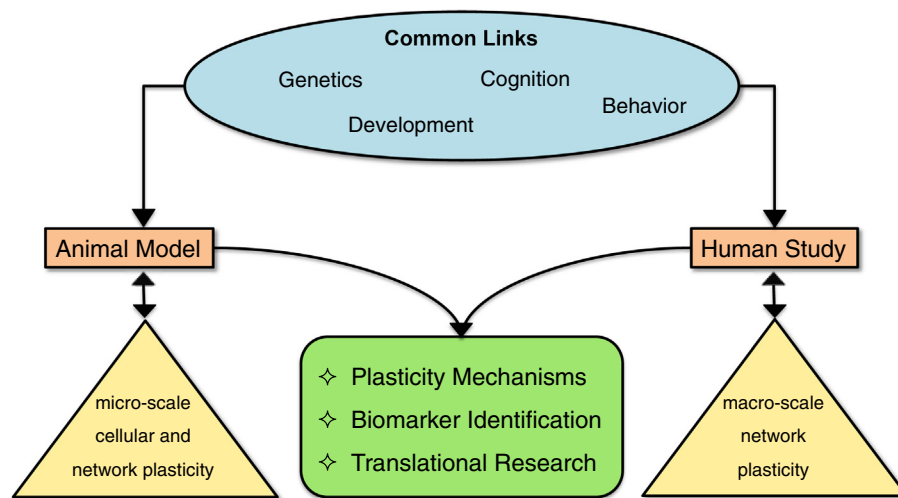


Fig. 6. The diagram encapsulates how cross-species studies inform neuroscience. Animal models and human studies are best integrated in research when they demonstrate conserved genetics, developmental profiles, and outcomes on specific cognitive and behavioral assessments (top row). In-depth investigations in animal models provide insights on micro-scale cellular and network plasticity (bottom left). Cellular activity profiles of both neurons and glia are measured using immunohistochemistry and slice and in-vivo electrophysiology (synaptic currents, firing rates, spike-field and LFP coherence). Human research incorporates neuroimaging, EEG and MRI, which inform macro-scale whole brain neural network dynamics (bottom right). Comprehensive and converging findings provided by these methods contribute to discovery of neuroplasticity mechanisms, identification of biomarkers that can be used to assess efficacy of targeted interventions and to the development of mechanistic interventions in translational research (center).

neuro-cognitive assessments developed in these cross-species studies as biomarkers, are only mildly impacted by a new intervention, then it urges informed iterative improvement of the intervention. In every way, building comprehensive knowledge of underlying neural mechanisms using cross-species research models is a win-win for interventional research. At the same time, we must not only take advantages of the converging findings across species, but also be aware of the dissimilarities in network complexity and in experimental protocols and not over-interpret outcomes.

Conclusion

Here, we have presented a case for the usefulness of cross-species neuroscience research in uncovering mechanisms of neuroplasticity and informing novel targeted interventions. In our opinion, such research is especially critical for the future of translational neurosciences. Engaging in cross-species research is challenging, as it requires collaborations between neuroscientists with diverse expertise. Yet, it is this diversity of knowledge that spurs innovations, and we urge the initiation of more studies using the cross-species research model.

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