Enhancing Cognition through Pharmacological and Environmental Interventions: Examples from Preclinical Models of Neurodevelopmental Disorders

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Abstract

In this review we discuss the role of environmental and pharmacological treatments to enhance cognition with special regards to neurodevelopmental related disorders and aging. How the environment influences brain structure and function, and the interactions between rearing conditions and gene expression, are fundamental questions that are still poorly understood. We propose a model that can explain some of the discrepancies in findings for effects of environmental enrichment on outcome measures. Evidence of a direct causal correlation of nootropics and treatments that enhanced cognition also will be presented, and possible molecular mechanisms that include neurotrophin signaling and downstream pathways underlying these processes are discussed. Finally we review recent findings achieved with a wide set of behavioral and cognitive tasks that have translational validity to humans, and should be useful for future work on devising appropriate therapies. As will be discussed, the collective findings suggest that a combinational therapeutic approach of environmental enrichment and nootropics could be particularly successful for improving learning and memory in both developmental disorders and normal aging.

Keywords: Cognitive impairment, nootropics, environmental enrichment, neuro developmental disorders, Ras-ERK pathway

I. Introduction

Cognitive impairment affects a significant part of the population (~ 1 in 20 people in the United States)(NIH, Center for Disease Control). Apart from the direct effects of the impairments on the individual and their ability to function in society, there are also significant emotional and financial burdens on family members, and increased costs for education, health care, and personal care. As a result, there has been a concerted effort to develop therapies that can benefit people with cognitive impairment. Because impairments to cognition can arise from a number of factors including gene defects as occurs in some neurodevelopmental disorders, adult related diseases, injuries, or with normal aging, some therapies may be too restricted (i.e., targeting a specific protein associated with a gene defect) and only useful for some types of cognitive problems associated with these conditions. However, it is possible that other types of therapies may generalize to several types of disorders or conditions associated with cognitive dysfunction and may be useful for both mild and sever forms of dysfunction. It is expected that these types of therapies would have their primary actions on fundamental pathways that are known to subserve learning and memory and other aspects of cognition.

The DSM-5 (Diagnostic and Statistical Manual of Mental Disorders 5th version) defines six neurocognitive domains: perceptual and motor function, language, learning and memory, social cognition, attention and executive function (Sachdev et al., 2014). Cognitive abilities are given by the sum of these domains or, more accurately by the functional sum of each subdomain: 1) Visual perception, visuo-constructional reasoning, perceptual and motor coordination, 2) Object naming, word finding, verbal fluency, grammar and syntax and receptive language, 3) Free and cued recall, recognition memory, semantic and autobiographical (episodic) memory and implicit learning, 4) Recognition of other individual's emotions and intentions, 5) Sustained, divided or selective attention and speed of processing, and 6) Planning and decision-making, working memory, inhibition and flexibility. Obviously, these domains do not work in an isolated fashion but as a complex and integrated system and lay on the very same substrate, the CNS. Hence a great deal of understanding and insight has come from pathological manifestations involving the CNS. Moreover, convergent pieces of information have pointed scientists to different strategies to enhance cognition for both the pathological and the healthy individual. Of these approaches, environmental enrichment and pharmacological

strategies that target well-described signaling pathways critical for synaptic plasticity and learning are particularly compelling.

This review will first cover considerations of behavioral approaches that are being used in preclinical research for higher-order cognitive domains such as executive functions, attention, working and episodic memory, and social skills targeted for assessing the effects of drugs or gene functions. Then, a working model will be presented aimed towards explaining how environmental enrichment can have different effects in mutant mouse models of disorders. We will offer an example of how environmental enrichment rearing for the fragile x model mouse results in some positives outcomes for synaptic plasticity but also reveals greater morphological deficits for dendritic spines than previously described. Recent work using a class of nootropics that positively modulate AMPA receptors (Ampakines), and increase neurotrophin levels, for improving several features of associated with aging including declines in neuronal health, synaptic plasticity, and behavior will be discussed. Finally, other work on a neurotrophin associated Ras-ERK pathway that is an important biological translator of environmental adaptations will be presented, as well as recent drugs that target it. A common thread for the effects of the nootropics that will be described is that they work on key points in at least one converging pathway involved in cognition.

II. How to Address Higher-Order Cognitive Dysfunctions in Preclinical Research with Clinical Translational Validity

Despite the fact that language is a characteristic cognitive domain of the human species, although some language-like functions have been mimicked in rodents (Haddon and Killcross, 2007), much of our knowledge comes from pre-clinical studies investigating the other 5 cognitive domains. Doubtlessly, understanding higher cognitive functions often presents the biggest challenge as it has some hidden pitfalls. Let us make the example of an archer whose objective is to strike an arrow to hit a moving target. Its success will depend on: its ability to hold the bow steady, its sight and only finally on its cognitive ability to generate and update a visuospatial map to calculate the arrow trajectory. A similar approach should be used to better interpret preclinical studies (Figure 1). Thus, it goes without saying that when a manipulation (e.g. a mutation, a drug or a treatment) gives for an instance a motoric manifestation, this will indeed affect spatial memory performance, whether or

not higher cognitive functioning is preserved. A similar effect on anxiety and other behaviors would also be expected (Bannerman et al., 2014). This of course does not imply that there could not be deficits in higher cognitive functioning without physical conditions nor that anxiety is required for these deficits to manifest.

Cognitive impairments in neurodevelopmental disorders are early features (Elvevag and Goldberg, 2000; Goldman-Rakic, 1994; Owens and Johnstone, 2006; Papaleo et al., 2012), long-lasting traits and strong prognostic predictors of patients' functional outcomes in the everyday life (Linsell et al., 2015; Troyb et al., 2016). Thus, cognitive deficits have some of the most critical impact on patients, their families and the entire public health system (Dziwota et al., 2018; Klietz et al., 2018; Lee et al., 2017; Mueser and McGurk, 2004). Notably, therapeutic interventions aimed towards cognitive deficits are still non-optimal, presenting huge variable responses between patients. Furthermore, the most largely used drugs for these disorders, such as antipsychotic drugs produce only small neurocognitive improvements if considering the entire population. Again, cognitive responses to antipsychotic drugs show marked inter-individual variability, and the mechanistic basis of such unpredictable variability is still scarcely known.

The development of more efficient treatments for cognitive disabilities are difficult to implement also because we still have an incomplete understanding of the heterogeneity, risk factors, neural circuitry and related mechanisms involved. This is particularly difficult to dissect in the clinical setting where a number of factors increase the complexity of the interpretation of the results including, for example, genetic/clinical heterogeneity, gene-by-gene, gene-by-environment and gene-by-environment-by-pharmacological treatments interactions. In this context, *in vivo* mechanistic studies in mouse models can be informative. In particular, genetic, environmental and pharmacological factors can be strictly controlled and available cutting-edge genetic tools allow for addressing mechanisms in a very high circuit- and cell-specific manner. In mouse models, environmental, genetics, developmental factors and all their interactions can be strictly controlled. Moreover, a number of fast-growing mechanistic tools are available to sort out causal relationships between phenotypes studied (e.g. classical, time- and site-specific conditional knockouts/knockins and transgenics, ENU, CRISPR, TALENs, ZFNs, chemogenetics, optogenetics). However, cognitive studies in rodents must not rely only on classical and easier assessments but must adopt properly designed tasks

with high predictive and translational validity in human clinical studies. In this sense, the best proof of predictive/translational validity is to assess healthy human subjects and/or human patients in equivalent tasks that are suggested to be modeled by the rodents' studies and confirm a similar outcome. Of course, we should be always cautious in not anthropomorphizing too much the observations made about mouse behavior, but it is mandatory to try to integrate, as much as possible, findings from rodents with equivalent human evidence. Otherwise, there is the risk that the mere use of too simplistic and often inappropriate behavioral tasks in rodent studies, despite very elegant and complex molecular and circuit-based techniques adopted, might fall short in its clinical impact. This has been part of the major causes of many clinical trial failures, and the related withdrawal of a number of pharmaceutical companies from neuroscience research (Nutt and Goodwin, 2011).

In the following sections, we will illustrate some approaches in preclinical research that we believe are better suited to address higher-order cognitive domains such as executive functions as defined by the NIMH Research Domain Criteria (RDoC), working and episodic memory, attentional control, and social cognition. These are all cognitive functions particularly disrupted in neurodevelopmental disorders (Barch and Ceaser, 2012; D'Souza and Karmiloff-Smith, 2017; Leavitt and Goldberg, 2009; Lesch, 2014, 2016; Mahdi et al., 2018; Ouhaz et al., 2018; Ross et al., 2006). This kind of classification is in line with, and expands previous reviews on, the topic of how to address cognitive deficits with cross-species validity (Cope et al., 2016b).

Cognitive control

Cognitive control abnormalities, also termed under the umbrella "executive functions", are among the main key features of neurodevelopmental disorders such as autism spectrum disorder (ASD), Intellectual Disability (ID), attention deficit hyperactivity disorder (ADHD) and schizophrenia (Boxhoorn et al., 2018; Conzelmann et al., 2016; Ehlis et al., 2011; Filipe et al., 2018; Garon et al., 2018; Hronis et al., 2017; Joyce et al., 2002; Karalunas et al., 2018; Kerns et al., 2008; Lifshitz et al., 2016; Managó et al., 2016; More and Jensen, 2014; More et al., 2017; Ouhaz et al., 2018; Scheggia et al., 2014; Sidorov et al., 2018; Weinberger et al., 1986). Cognitive control deficits also are described for individuals with prefrontal

cortex lesions suggesting that the frontal lobe system area is critically important for this behavior (Miller and Cohen, 2001).

Experimentally, cognitive control can be measured by so-called “attentional set-shifting tasks”. A classic and widely used task is the Wisconsin Card Sorting Task (WCST) (Berg, 1948; Eling et al., 2008), while a more recent and refined task is the “intra- and extra-dimensional attentional set-shifting” of the Cambridge Neuropsychological Test Automated Battery (CANTAB) (Barnett et al., 2010; Roberts et al., 1988) (Table 1). Impairments in the ability to shift an attentional set (measured by Extra Dimensional Shift stages) are sensitive measures of frontal cortices-related executive control deficits. (Owen et al., 1993; Scheggia et al., 2014; Scheggia et al., 2018). The human WCST and Intra Dimensional/Extra Dimensional tasks have been successfully modeled and validated in rodents (rats and mice) confirming that the measures of cognitive control assessed rely on mostly conserved neural substrates in humans, monkeys, rats and mice (Birrell and Brown, 2000; Bissonette et al., 2008; Brown and Bowman, 2002; Dias et al., 1996; McAlonan and Brown, 2003; Owen et al., 1993; Rahman et al., 1999; Robbins, 2007; Roberts et al., 1988; Scheggia et al., 2014). The first example of such a task in rodents was the so-called attentional set-shifting “digging task”, developed for rats and then validated for mice (Birrell and Brown, 2000; Bissonette et al., 2008; Papaleo et al., 2008). An automatic version of the task is now available that reduces time, increases reliability, replicability, and standardization, and is useful for large-scale genetic and/or drug-screening studies with proven predictive validity in healthy human and patients with schizophrenia studies (Scheggia et al., 2014; Scheggia et al., 2018).

Working memory

The definition of working memory regards the type of memory that is active and relevant only for a short period of time, while performing complex tasks such as reasoning, comprehension and learning. The major components of working memory implicate a short-term memory storage and a complex multimodal manipulation of these memories in order make an action based on a determined rule or need (Baddeley, 2010; Managó et al., 2016; Scheggia et al., 2012).

Several paradigms are used to test working memory functions in humans with the most used being the N-Back task (Callicott et al., 2000), and the spatial delayed response tasks (Barch et al., 2012). Equivalent tasks employed in rodents with high

translational efficacy of preclinical into clinical data, include the T-maze discrete paired-trial variable-delay alternation task, the 8-arm radial maze “delayed non-match to sample” or ‘‘win-shift’’, the 8-arm maze “random foraging task”, the odor span tasks, and some paradigms of delayed matching and delay non-matching to sample position operant conditioning tasks (Aultman and Moghaddam, 2001; Dudchenko, 2004; Dunnett, 1993; Floresco et al., 1997; Kellendonk et al., 2006; Papaleo et al., 2014b; Papaleo et al., 2008; Papaleo et al., 2012; Sannino et al., 2015; Seamans et al., 1995; Seamans and Phillips, 1994; Young et al., 2007). Data gathered from mouse studies in these tasks have proven to be predictive of equivalent human findings. For example, using the T-maze discrete paired-trial variable-delay alternation task in mouse models, it has been shown that a very similar mouse-human functional non-linear epistatic interaction between the catechol-O-methyl transferase (COMT) and dysbindin-1 genes was evident at the level of activity in the prefrontal cortex in healthy human subjects performing a N-Back working memory task (Papaleo et al., 2014a, b; Papaleo et al., 2008).

Similarly, this specific T-maze paradigm predicted COMT-by-sex-dependent interactions in healthy subjects performing the N-Back working memory task and related cortical anatomy (Papaleo et al., 2014b; Sannino et al., 2015). To note, genetic human effects in the N-Back task performance correlated with genetic mouse performance in the discrete paired-trial T-maze testing with variable delays between 4 and 60 seconds (Papaleo et al., 2008) and (Sannino et al., 2015), as well as the acquisition itself of the task with an inter-trial delay of 4 seconds (Papaleo et al., 2014a). Effects on the acquisition of this specific discrete paired-trial alternation task are likely due to the link between working memory and prefrontal cortex function (Kellendonk et al., 2006). While not exhaustive, these examples provide evidence of efficient approaches for more predictive translational research.

Episodic Memory

Episodic memory is the memory of events and experiences that can be recalled in relation to a specific time and in proper order (Tulving, 2002). The main components of episodic memory are, in an integrated way, the “what”/”who”, “when”, and “where” (WWW) a past experience occurred. This is distinguishable from the other form of

declarative memory, semantic memory that is the type that refers to conceptual information and general facts. For humans, episodic memory can be investigated using interview or self-report, although this can be problematic in individuals with disorders/diseases that affect their ability to verbally communicate since scoring depends on a high amount of detail (Ben Shalom, 2003; Cheke and Clayton, 2013). Thus, a number of tests have been used in human studies most of which are WWW retrospective and prospective tests (Loftus and Davis, 2006).

Episodic-like memory in rodent studies also has been extensively assessed using WWW tests (Dere et al., 2005; Kart-Teke et al., 2006). Combining neuroanatomical methods with the WWW tests also have been useful for delineating the involvement of brain structures to the specific components of this type of memory (e.g., hippocampus is needed for “what”, “when”, and “where”, whereas medial prefrontal cortex is needed only for “where”) (DeVito and Eichenbaum, 2010). Another task that is often used to capture the animal’s awareness of the relationship between objects (what) and their spatial locations (where), is the hippocampal-dependent Object Location task (Barker and Warburton, 2015). This task has been used in numerous studies evaluating mouse models of cognitive disorders, including developmental and aging-related disorders, and preclinical testing of therapies therein (Contestabile et al., 2013; Contestabile and Sintoni, 2013; Karamihalev et al., 2014; Manago et al., 2016; Ricciarelli et al., 2017; Seese et al., 2014b; Seese et al., 2014c). Finally, with regard to disorders, it is important to consider that deficits in episodic memory can reflect impairments either in the encoding or the retrieval of the information. Therefore, the inclusion of tasks that examine how animals sample the environment during learning may also be useful for preclinical studies. To this end learning paradigms which are self-directed, non-reinforced, and allow for the assessment of an animal’s behavior in relation to different aspects of the environment over time may be particularly useful.

Attention

Attentional control is the ability to select specific available cues for preferential processing, while ignoring competing information (Smid et al., 2006). There are different subtypes of attention such as sustained attention, selective/focused attention and divided attention (Millan et al., 2012). Common available tasks to measure attentional abilities in humans are the Continuous Performance Test (CPT)

(Cornblatt et al., 1988; Gold et al., 2012; Gold and Thaker, 2002; Nuechterlein and Dawson, 1984), the CPT-Identical Pairs (CPT-IP) (Cornblatt et al., 1988), the A-X CPT versions (Servan-Schreiber et al., 1996), the Stroop task (MacLeod, 1991; Stroop, 1935; Zvyagintsev et al., 2013) and the Spatial Attentional Resource Allocation Task (SARAT) (Hahn et al., 2006a). For rodents, discrete elements of attentional processes such as sustained and focused attention, impulse control, perseverative and reactivity-related functions can be effectively studied. In particular, one of the most effective and extensively used task in rodents is the 5-Choice Serial Reaction Time Task (5-CSRTT) which allows for measures of general attention, impulse control and processing speed (Carli et al., 1983; Ciampoli et al., 2017; Huang et al., 2017; Mereu et al., 2017; Robbins et al., 1993; Robbins, 2002; Voon et al., 2014). Conversely, the Distractor Condition Sustained Attention Task (dSAT) and the 5-Choice Continuous Performance Test (5C-CPT) are operant –based tasks developed as signal-detection tasks first in rodents (Barnes et al., 2012; Bushnell, 1999; Ciampoli et al., 2017; Huang et al., 2017; McGaughy and Sarter, 1995; Mereu et al., 2017; Mohler et al., 2001; Nuechterlein et al., 2009; Young et al., 2009) and then redesigned for humans, providing clinical translatability (Demeter et al., 2008; Young et al., 2013). Similarly, based on the proven utility of the SARAT paradigm in distinguishing deficits in selective attention from broad monitoring alterations relevant to schizophrenia (Hahn et al., 2012; Hahn et al., 2006b), equivalent tasks have been developed in both adult and adolescent mice (Ciampoli et al., 2017; Huang et al., 2017; Mereu et al., 2017). Overall, all of these tasks represent useful tools for bridging preclinical and clinical research focused on attention.

Social Cognition

Fundamental to all social interactions, the mutual understanding of social information is primarily achieved with *the ability to perceive, process and interpret facial and body expression of emotions*. This biologically innate ability, defined as “social cognition”, has a widespread implication in the development of social connection and cooperation, in the evaluation of truthfulness/deception, in shaping individual success and personal care, and in national security and intelligence. Social skill domains can be categorized into emotional processing, social perception, social knowledge, theory of mind and attributional bias (Billeke and Aboitiz, 2013; Green

and Horan, 2010; Green and Leitman, 2008; Green et al., 2005; Green et al., 2008; Managó et al., 2016; Millan and Bales, 2013).

Emotion recognition tasks are the most-extensively used paradigms to assess human social cognition (Green et al., 2015; Henry et al., 2016; NIH). Due to the high complexity of the measures used to study social cognition in humans it is difficult to create translationally-valid tasks for rodents. Nonetheless, mice are a social species that exhibits complex social behaviors hence measures of social ability are often taken from home-cage observations such as maternal/parental behaviors, colony formation/hierarchy, interactions between peers, nest-building, sleeping together in the nest or resting in group huddles (Green et al., 2005; Millan and Bales, 2013).
Moreover, the basic assessment of social interaction abilities in rodents involves measurements of specific behaviors such as sniffing, following, climbing on, ultrasonic vocalizations, allogrooming, fighting, and sexual behavior while two unfamiliar adults freely interact in an open-field arena (Bambini-Junior et al., 2014; File and Hyde, 1978; File and Seth, 2003; Hirsch et al., 2018; Huang et al., 2014; More, 2008; Silverman et al., 2010). Under these settings, many genetic, pharmacological, developmental and neurobiological rodent models have been shown to exhibit perturbations in social interaction (Hida et al., 2013; Koros et al., 2007; Millan and Brocco, 2008; Peleg-Raibstein et al., 2012; Pratt et al., 2012; Sams-Dodd, 1999). These social interaction abnormalities are usually interpreted to be relevant to the social withdrawal phenotypes associated with developmental disorders including ASD, depression and schizophrenia. Beyond this, other studies have explored the possibility of testing more specific social cognition endophenotypes such as the animal's ability to encode, retrieve/recognize and respond appropriately to social stimuli (Millan and Bales, 2013; Silverman et al., 2010). Such tasks may provide more relevant information on social deficits present in neuro-developmental disorders.

In general though, sociability in rodents is widely tested using the three-chamber task (Crawley, 2000; Kaidanovich-Beilin et al., 2011; Moy et al., 2007; Papaleo et al., 2011; Roullet and Crawley, 2011; Young et al., 2011). Another widely used procedure is the "habituation/dishabituation" paradigm (Dluzen and Kreutzberg, 1993; Huang et al., 2014; Winslow and Camacho, 1995). Moreover, social motivation components can be tested in operant chambers, where a rodent is trained to press a lever with access to a conspecific as a social reinforcer (Evans et al., 1994).

However, despite their extensive use, most of these tasks are limited in their equivalence to human clinical tasks to address social cognition. The evaluation of social cognitive processes such as theory of mind, facial perception/recognition, and gaze-following are tested in non-human primates (Machado and Nelson, 2011; Millan and Bales, 2013). A notable exception is a few seminal studies that did show the transmission of pain/fear responses from one rodent to a familiar observer (Burkett et al., 2016; Langford et al., 2006; Pisansky et al., 2017; Sterley et al., 2018), reminiscent of empathy or consolation, or social buffering. However, consistent efforts in the field are still required with a clear aim to prove the predictive translational validity of novel and more refined social cognitive tasks in rodents.

III. The Importance of Assessing Developmental Trajectories

Higher order cognitive functions exhibit different trajectories through the life-span, from their establishment and maturation during development through their decline with age (Gutchess, 2014). For example, significant improvements in higher-order cognitive functioning appear from childhood to adolescence, with the most significant changes in the development of attentional control, processing speed, decision making, planning, and response inhibition (Anderson, 2001; Brodeur and Enns, 1997; Casey et al., 2008; Davidson et al., 2006; Deoni et al., 2011; Ernst et al., 2011; Gold and Thaker, 2002; Rosso et al., 2004; Yurgelun-Todd, 2007; Zvyagintsev et al., 2013). On the other hand, in the course of normal aging there are marked declines in cognition including deficits in working memory and long-term memory (Park and Reuter-Lorenz, 2009). Because of these age-related changes in behavior, there are several things that must be considered with regard to assessing the efficacy of treatments, including both pharmaceutical and environmental enrichment approaches. First, when should treatments commence (i.e., at what age, that also would not have negative effects particularly for drug therapies) and how long should they be given? Are multiple treatments needed for greater outcomes? Importantly, what endpoint measures should be assessed that are the most informative? These fundamental questions are often difficult to address in a single study, primarily because they involve many variables that need to be controlled. Another key problem that investigators face is understanding how the anatomical, physiological, and behavioral changes that normally occur with development and aging relate to

each other, as a basis for then investigating how they are influenced by such things as pathology and genetic mutations, as well as potential treatments.

In the context of neurodevelopmental disorders, it is important to note that many are known to be caused by, or highly associated with, genetic mutations (Kasem et al., 2018; Leung and Jia, 2016; Penagarikano et al., 2007; Ramaswami and Geschwind, 2018; San Martin and Pagani, 2014). Genetic variations can severely impact brain maturation (e.g., dendritic morphologies and spine densities, cell number) and related developmental processes (including cognition) that ultimately result in the appearance of psychiatric-related behavioral dysfunction. For example, for genetic risk conditions such as the 22q11.2 deletion syndrome (with high penetrance of ADHD and schizophrenia) specific neurocognitive developmental lags across different ages have been found, consistent with greater gray matter loss and accelerated cortical thinning during childhood and adolescence (Eliez et al., 2000; Gothelf et al., 2008; Gur et al., 2014; Jalbrzikowski et al., 2013; Kates et al., 2004; Kates et al., 2001; Schmitt et al., 2015; Simon et al., 2005). In addition, a number of longitudinal clinical studies have demonstrated abnormal cognitive processes that were correlated with cortical maturation pathologies in other disorders such as ASD and schizophrenia. These include psychomotor and ideomotoric functioning, verbal processes, perseveration, cognitive rigidity, attention and perception (Docx et al., 2014; Eliez et al., 2000; Gothelf et al., 2008; Jalbrzikowski et al., 2013; Karalunas et al., 2017; Kates et al., 2004; Kates et al., 2001; Moffitt et al., 2015; Muetzel et al., 2018; Sannino et al., 2017; Schmitt et al., 2015; Simon et al., 2005). To further complicate the picture is some recent evidence indicating that people with schizophrenia, although they do not exhibit delay-dependent deficits (Gold et al., 2010), have impairments in selective attention, working memory and executive function that seem to represent distinct defects instead of different manifestations of one higher-order impairment. Although measures of top-down control of selective attention, working memory and executive function seem all intercorrelated, substantial evidence indicates that working memory and executive function are separate sources of variance (Gold et al., 2018).

These findings have increased emphasis on the need to assess developmental trajectories for various disorders relative to controls with the hope of better refining diagnostic and intervention strategies, and possibly identifying pertinent markers for early interventions.

In contrast to human work, preclinical rodent studies assessing developmental trajectories in relation to genetic vulnerability factors are more limited. Most often, animal work relies on using genetically engineered mutant mouse lines that are generally treated and then evaluated or tested in adulthood. Moreover, treatment interventions are most often given to animals in adulthood when the abnormal phenotype is fully developed, rather than during early critical developmental periods when neuronal connections are being wired, and thus more likely to be malleable and responsive to treatments. As stated above, understanding the changes that occur during development, and how a specific gene defect affects this, is crucial for deciding when to assess pharmacological and environmental strategies for enhancing cognition in the context of neurodevelopmental disorders with a high genetic component. In addition, it is important to note that apart from genetic defects, many other types of manipulations have been used to show that a vast array of early developmental challenges result in profuse long-term neural and cognitive effects (such as on dendritic spine density, brain volume, and attention and working memory) that last well into adulthood; when delayed or presented in adulthood, similar manipulations have less pronounced effect. Such manipulations include brain insults during gestation, parturition or the early postnatal period, as well as altered maternal care and post-weaning isolation, maternal malnutrition and vitamins deficiencies, or early pharmacological treatments (Cope et al., 2016a; Cope et al., 2016b; Lipska et al., 2002a; Lipska et al., 2002b; Lipska et al., 1992; Lipska et al., 2001; Pennucci et al., 2016).

Another key factor in preclinical work that one needs to consider when assessing the ontogeny of higher-order cognitive functions in rodents are the tools, which need to accommodate the more limited developmental windows in rodents as compared to humans. Important available tools are developmental milestones assessments developed for mice (Ricceri et al., 2004; Scattoni et al., 2006; Scattoni et al., 2009; Scattoni et al., 2005), which give basic knowledge on development of physical features. In relationship to higher order cognitive functions, some recent implementation of the 5CSRTT for adolescent mice could be useful for assessing control of attention (Ciampoli et al., 2017; Remmelink et al., 2017; van Enkhuizen et al., 2014). However, other work is needed to better develop the preclinical battery of tasks able to consistently address higher order cognitive function development in adolescent and pre-adolescent rodents.

Finally, with regard to pertinent treatments for neurodevelopmental disorders, it is important to consider the genetics of individual patients rather than the overall heterogeneous population, similar to what has been already achieved with chemotherapeutic strategies in cancer genomics for personalized medicine (Boyer et al., 2016; Hermens et al., 2006; Jellen et al., 2015; Lim et al., 2015; Riazuddin et al., 2017). Genetic factors are known to play a critical role in a variety of behaviors, including cognition and the pathogenesis of psychiatric illnesses (Bespalov et al., 2012; Bespalova and Buxbaum, 2003; Papaleo et al., 2012; Scheggia et al., 2018). Moreover, genetic variations can also moderate the variable responses to pharmacological and intervention strategies based on both pharmacodynamics and pharmacokinetics mechanisms (Hanson and Madison, 2010; Hu, 2012; Siniscalco et al., 2012; Smoller, 2014). A recent example on this emerging field, and specifically related to cognitive control with mouse-human cross-species validation, is evidence that a common and functional genetic variation that reduces the expression of the dysbindin-1 gene stratifies subjects whose executive functions better respond to antipsychotics medications (Scheggia et al., 2018). Similar approaches should be explored and applied also in the context of developmental disorders, to deliver more effective intervention strategies.

IV. Genes and Environment: Towards a Model for Effects on Behavior

Epigenetic mechanisms dynamically regulate the transcription and expression of genes throughout life and are responsive to environmental changes. The transcription of DNA into mRNA is influenced by epigenetic marks that are abundant both inside or around these genes regions; DNA methylation and histone modifications are the most studied epigenetic processes, but also noncoding RNAs including microRNAs have a substantial role (Akbarian and Huang, 2009; Moore et al., 2013; Pishva et al., 2014; Yu et al., 2012). Current evidence suggests that these epigenetic processes can be altered by life experiences such are environmental and social rearing conditions. For example, in a recent study, young mice that had experienced two months of environmental enrichment were found to have regionally specific effects on DNA methylation and transcription within hippocampus (Zhang et al., 2018).

As expected from epigenetic modifications, it is clear that environmental enrichment leads to marked changes in gene expression in brain. One of the best

examples of this is for the Brain derived neurotrophic factor (BDNF), in which increases in both mRNA and protein for this neurotrophin have been observed in hippocampus and other brain regions of animals exposed to environmental enrichment (Baroncelli et al., 2010; Cowansage et al., 2010; Nithianantharajah and Hannan, 2006; Simpson and Kelly, 2011a). BDNF, acting via the TrkB receptor, promotes dendritic growth and increases spine density in an ERK1/2-dependent manner (Cowansage et al., 2010). Thus, many of the effects of environmental enrichment such as increased dendritic spinogenesis, enhanced synaptic plasticity (both Long-term potentiation and Long-term depression), and increased learning and memory and cognitive flexibility could be due to increases in BDNF protein content and enhancement of BDNF-trkB signaling; other findings using BDNF heterozygous mice further supports this idea (Novkovic et al., 2015; Rossi et al., 2006).

While it is widely known that environmental enrichment enhances cognition and dendritic spine density in mammals (Correa et al., 2012; Fischer, 2016; Hakansson et al., 2017; Karelina et al., 2012; Sampedro-Piquero and Begega, 2017; Sansevero et al., 2016; Schuch et al., 2016), the contributions of the various aspects of the environment are not well understood for each phenotype that has been studied. Environmental enrichment typically is comprised of three domains being (I) increased physical activity, that is usually provided by a running wheel and a bigger house cage, (II) increased social groupings, and (III) increased opportunities for exploration (i.e. larger environments relative to standard housing conditions) and interactions with novel objects such as toys (Sztainberg and Chen, 2010; Wood et al., 2011). Of these components of environmental enrichment, some have shown that increased physical activity per se seems to provide most of the beneficial effects (Brown et al., 2003; Kobilo et al., 2011; Lazarov et al., 2010; van Praag et al., 1999, 2000). Although lifelong enrichment in the absence of exercise also has profound effects on reversing age-related declines in recognition, spatial and working memory (Birch and Kelly, 2018), suggesting that both the social and somatosensory components also contribute to the positive effects of enrichment. Finally, the effects of social versus the non-social (novelty, exercise, etc.) components of enrichment are also dissociable by several measures including brain weight that is more responsive to environment complexity than social conditions (Rosenzweig et al., 1978), and differential effects on impulsivity, behavioral flexibility, and memory (Prado Lima et al., 2018; Wang et al., 2017).

In spite of the overall effect that environmental enrichment can have, the fundamental designs used by laboratories for social, physical, somatosensory enrichment are generally not uniform. Studies also often differ in animal strain, sex, and types of controls used (e.g., isolated vs group standard-housed controls) (for full review, see (Simpson and Kelly, 2011b)) that can further complicate findings and lead to varied outcomes between laboratories. It cannot be overstated that for any experimental design, consideration of the control groups is paramount; for enrichment paradigms, differences between control animals that have been socially isolated versus those that have social experience from group housing needs to be considered since this may confound interpretations of the social vs non-social aspects of the enrichment effects. Furthermore, another complication to many preclinical studies assessing the effects of enrichment on a mouse model of a disease or disorder, is the specific manipulation of the genome in a mutant mouse model. It is not surprising then that studies have given ambiguous and often contrasting results on the efficacy and effectiveness of interventions and therapies performed in mouse mutants to human conditions (Ciammola et al., 2017; Daumas et al., 2017; Gao et al., 2018; Shi et al., 2017; Woodbury-Smith et al., 2017). While these discrepancies might indeed be attributed to the dramatic epigenetic modifications as described above, it does not fully explain the differences across laboratories.

Based on these issues, we propose a working model that the degree of response to environmental enrichment is limited by (I) the underlying neurobiology of the experimental subjects (i.e., control vs genetic mutation, or disease state) and (II) the variations in the type and amount of enrichment. Thus, differences in either of these two components might have very different outcome on cognitive functions. This model is more heavily influenced by the different computational power between a functional CNS and that one of a relevant mutant, than enrichment itself. For example, in the case of ID in which processing of environmental information or cues are perturbed, this subject's capacity for processing experiences in a mild enrichment paradigm may already be at its maximal limit. Thus, any further increase in the type of level of enrichment would not have any further effect in the mutant as compared to wild type (Figure 2). On the other side of the spectrum, any long-lasting stress-induced increase in cortisol levels could have deleterious effects that outweigh any genetic resilience (Barfield and Gourley, 2018). However, an

impoverished environment might also elicit genotype differences depending on the genetic mutations and whether the specific gene affected in the mutant offers resilience to such conditions in the wild type. This idea is borne out for a model of non-syndromic ID, the Gdi1-null mouse, which did not show the expected cognitive impairment when housed in mildly enriched environments but only when housing was a mildly impoverished environment (Bianchi et al., 2009; D'Adamo et al., 2014; De Giorgio, 2017). This may be explained by the neurobiology of the Gdi1-null mutant that curtails the benefit it can get from environmental enrichment, in spite of an increased number of dendritic spines this environment elicits in the brain (Correa et al., 2012; Daumas et al., 2017; Hunter et al., 2017): In Gdi1-null mice the pre-synaptic recycling of glutamatergic vesicles remains time-limited, hence the beneficial effects of enrichment remain curtailed and ineffective on some sustained tasks (Bianchi et al., 2009; D'Adamo et al., 2014; Ezaki and Nakakihara, 2012; More et al., 2017; Strobl-Wildemann et al., 2011). Finally, it is important to note that the proposed outcomes of this model also would be influenced by the age at which enrichment began, and the duration of exposure. To this point, studies suggest that the effectiveness of enrichment increases when provided early in life and with long duration (Freret et al., 2012; Simpson and Kelly, 2011a).

In consideration of this working model to explain effects of environmental enrichment, both syndromic and non-syndromic rodent models of ID are the most prominent examples for the physiological limitations in the response to different forms of enrichment (D'Adamo et al., 2014). In the following section we will describe one of these cases for ID, the Fragile X mouse model, and the influence of environmental enrichment on dendritic morphology and synaptic plasticity.

Environmental enrichment treatment in the Fragile X syndrome mouse model: an example

Fragile X syndrome (FXS), the most common form of inherited ID, is generally caused by an expansion of CGG-repeats in the *Fmr1* gene that encodes Fragile X Mental Retardation Protein (FMRP) which silences the gene (Penagarikano et al., 2007). FMRP has been shown to regulate protein synthesis in dendritic spines, and its loss results in abnormal levels of many synaptic proteins (Chen et al., 2010; Muddashetty et al., 2007; Schütt et al., 2009; Todd et al., 2003; Zalfa et al., 2003). Aligning with the synaptic protein defects, a well-described feature of FXS is the

presence of “immature” dendritic spines in neocortex. Specifically, pyramidal cell dendritic spines are more numerous, with a greater proportion being long and thin, than in cognitively normal individuals (Hinton et al., 1991; Rudelli et al., 1985). As spines are thought to be the site of functional changes that mediate memory storage, an immature morphology could represent the critical effect of the FXS mutation underlying learning impairments in this disorder. If this is the case, then the degree to which the spines are adaptable to morphological change and can be driven towards maturation in the FXS condition is an important question to explore for developing strategies to improve cognition and behavior.

The *Fmr1* knockout (KO) mouse model of FXS exhibits many phenotypes of the human condition including learning impairments (Brennan et al., 2006; Consortium, 1994; D'Hooge et al., 1997; Ventura et al., 2004; Zhao et al., 2005), greater impulsivity (Moon et al., 2006), and a predisposition for seizures (Chen and Toth, 2001; Musumeci et al., 2000; Yan et al., 2004). In addition, *Fmr1* KOs exhibit abnormally high numbers of long-thin spines and greater spine densities in neocortex (Comery et al., 1997; Galvez and Greenough, 2005; Hayashi et al., 2007; McKinney et al., 2005; Su et al., 2011) as seen in human studies. Consistent with the learning and spine morphology deficits, the mutants also have deficits in long-term potentiation (LTP) in both hippocampus (Hu et al., 2008; Lauterborn et al., 2007; Lee et al., 2011; Shang et al., 2009; Yun and Trommer, 2011) and cortex (Larson et al., 2005; Li et al., 2002; Meredith et al., 2007; Zhao et al., 2005). Because of the strong phenotypic correspondence between the human condition and the mouse model, the *Fmr1* KO has been widely used in the field to investigate the relationship between spine morphology defects, synaptic plasticity deficits, and learning impairments in the disorder, and for testing therapeutic strategies aimed at improving outcomes for individuals with FXS.

Much work in the *Fmr1* KO has focused on the hippocampal CA1 field where discrete LTP deficits have been reported (Lauterborn et al., 2007), and pronounced defects in the signaling mechanisms that regulate the spine actin cytoskeleton to support hippocampal LTP (Chen et al., 2010; Seese et al., 2012). In sum, loss of the FMRP protein results in defective signaling in the pathway involving the small GTPase Rac that engages p21-activated kinase to promote filamentous actin stabilization in dendritic spines (Chen et al., 2010; Lauterborn and Gall, 2017; Rex et al., 2009). Because of the signaling defect, LTP at these synapses is slow to

stabilize leaving it vulnerable to disruption for a longer period of time as compared to wild types (Chen et al., 2010; Lauterborn and Gall, 2017). Given these marked defects in the actin cytoskeleton machinery needed for synaptic reorganization in hippocampus, it is surprising that studies on dendritic spine abnormalities in this structure in the KO have been mixed (Bilousova et al., 2009; Braun and Segal, 2000; Grossman et al., 2006; He and Portera-Cailliau, 2012; Levenga et al., 2011; Pop et al., 2012; Segal et al., 2003; Su et al., 2011; Swanger et al., 2011).

To investigate the degree to which spine abnormalities occur in the adult *Fmr1* KO hippocampus, and to test whether spine morphologies might be normalized by environmental enrichment rearing as had been reported for neocortex (Meredith et al., 2007; Restivo et al., 2005), as study was conducted using 3-dimensional (3D) reconstructions of green fluorescent protein (GFP) expressing CA1 hippocampal neurons (Lauterborn et al., 2015). Beginning at weaning (21 days postnatal) KOs and wild types were either reared in an enriched environment or in standard laboratory cages until 3 months old; the enriched housing system consisted of multiple rooms, bedding, a habit trail system, running wheel, and other small objects. Analyses of CA1 hippocampal neurons revealed only modest differences between spine measures for *Fmr1* KO and wild type mice that were provided standard housing, with the exception of spine head volumes that were reliably lower in the mutants and consistent with findings for neocortical neurons (Irwin et al., 2000). Rearing in the enriched environment did not attenuate this difference; rather, it revealed greater effects of the FXS mutation on dendritic arborisations and spines of adult hippocampal neurons. Enrichment resulted in wild type mice exhibiting significantly greater numbers of higher order branching than did *Fmr1* KOs, although average dendritic lengths were similarly increased in both genotypes receiving environmental enrichment relative to standard housing. Rearing in enriched environment did not correct spine head volumes in the *Fmr1* KO: mean spine head volume was approximately 40% lower in KOs than in wild types under both housing conditions. However, rearing conditions did affect total spine length with enrichment normalizing mean spine length in the mutants. These findings suggest that with the FXS mutation certain spines features such as length may be more malleable to the influence of environment, whereas others such as spine head size are not. Given the strong correlative evidence that spine head volume and structure is coupled to synaptic function (Bosch and Hayashi, 2012; Lynch et al., 2007), these findings also

suggest that therapies which target spine actin cytoskeleton regulatory proteins may be particularly effective for FXS, and other developmental ID disorders characterized by spine morphology defects.

The above results suggest that rearing environment alone is not sufficient to overcome spine morphology defects in FXS. Yet, rearing environment and BDNF application each have been shown to influence the effect of the *Fmr1* mutation on LTP. In particular, *Fmr1* KO mice reared in an enriched environment reportedly have normal cortical potentiation, comparable to levels seen in wild type mice housed in standard cages (Meredith et al., 2007). This suggests that environmental enrichment might reverse or offset cellular disturbances underlying some impairments in synaptic plasticity and learning in the FXS mutants and in the human condition. The effects of rearing environment in the *Fmr1* KO on hippocampal LTP or hippocampal-dependent behaviors have yet to be tested. However, application of exogenous BDNF to hippocampal slices fully restores LTP in the mutants (Lauterborn et al., 2007), suggesting that drug approaches which enhance neurotrophin expression may be beneficial for treating hippocampus-dependent behaviors in individuals with the fragile X mutation. Ampakines are a good example of such an approach as they increase neuronal BDNF expression (see section below). While current work is testing this possibility in the mouse model, it is important to note that not all neurodevelopmental disorders may be amendable to this type of intervention. Notably, recent studies have shown that semi-chronic ampakine treatment in the BTBR mouse strain, that exhibits behaviors aligning with some of the major diagnostic criteria of ASD, did not improve their memory performance in the hippocampus-dependent object location task (Seese et al., 2014a).

A final important consideration with regard to treatment for neurodevelopmental disorders, as discussed earlier, is the age at which animals are exposed to environmental enrichment, and the length of exposure. It is clear for *Fmr1* KOs that environmental enrichment rearing beginning at weaning age was not sufficient to normalize spine measures. However, recent work has shown that early social enrichment starting at the time of birth rescued some behaviors and induced some maturational changes in CA1 hippocampal spines in the *Fmr1* KO (Oddi et al., 2015). More striking improvements on brain maturation and hippocampal function were reported for the Ts65Dn mouse model of Down Syndrome, another form of ID, following early enrichment with both enhanced social (maternal) care and a housing

environment that included options for exploration and physical activity, and novelty (Begenisic et al., 2015). Thus, early intervention may be key to better outcomes for individuals with developmental disabilities, and is consistent with a recent study describing positive outcomes for two young FXS children that received intensive educational interventions combined with several different drug treatments beginning at two years of age (Winarni et al., 2012).

V. A Pharmacological Approach Toward Improving Cognition

Cognitive function is ultimately dependent on its capacity for growth and establishing appropriate neuronal connections. There are many factors that play a role in this but, at minimum, it relies on sufficient neuronal activity and appropriate engagement of synaptic proteins and signaling cascades to promote the establishment and strengthening of synaptic contacts. Just as sensory stimuli from the environment ultimately have effects on brain through activation of neuronal circuits, one can take advantage of this by using drugs that enhance neuronal activity. One such example of this are ampakines, which have been shown to be cognitive enhancers (nootropics) and hold great promise as potential therapeutics for a number of conditions with memory impairment including Alzheimer's disease, Huntington's disease, schizophrenia, menopause, developmental intellectual disabilities, and aging. In the next section, we will focus on normal aging to illustrate how daily treatments with an ampakine in combination with environmental enrichment can forestall the deleterious effects of brain aging, with striking effects on neuronal cytoarchitecture and behavior.

Ampakines and Environmental Enrichment effects on brain ageing: an example

Positive modulators of the glutamatergic α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor were identified nearly 35 years ago as having positive effects on learning and memory in rodents, including in conditions of impaired cognition function (Cumin et al., 1982). Variants of these compounds (e.g., lower impact ones, such as CX516, that have greater safety) also have been tested in humans and evaluated in clinical trials for several different conditions including schizophrenia, mild cognitive impairment, and fragile X among others (Berry-Kravis et al., 2006; Boyle et al., 2012; Goff et al., 2001; Johnson and Simmon, 2002; Oertel et al., 2010; Wezenberg et al., 2007) (see also ClinicalTrials.gov). Ampakines are a

specific class of positive allosteric AMPA receptor modulators that have been shown to not only facilitate learning and the synaptic mechanisms thought to underlie memory formation (Lynch et al., 2014; Lynch and Gall, 2006), but also promote neurotrophin (BDNF) expression in forebrain and protect neurons from neurodegeneration (Bahr et al., 2002; Lauterborn et al., 2009; Lauterborn et al., 2000; Rex et al., 2006; Simmons et al., 2011).

Ampakines are small molecules that bind at the dimer interfaces of AMPA-type glutamate receptors (Jin et al., 2005) and modulate the ligand-bound receptors by slowing their deactivation and desensitization rates (Arai et al., 2000). Together, these two effects on the AMPA receptor prolong the open time of the ion channel and increase the amplitude and duration of fast, excitatory transmission (Lynch and Gall, 2006). The ampakine-induced enhancement of excitatory postsynaptic currents lowers the threshold for LTP, a form of synaptic plasticity thought to underlie learning and memory (Staubli et al., 1994). Moreover, in cases where LTP has been shown to be deficient such as in rodent models of Huntington's disease, Angleman syndrome, and low estrogen, treatment with certain variants of the ampakines markedly improves synaptic plasticity (Baudry et al., 2012; Kramár et al., 2012; Simmons et al., 2009). As predicted from the effect on LTP, ampakines have been shown to enhance learning in both healthy normal rodents (Hampson et al., 1998) and humans (Ingvar et al., 1997), as well as in models of cognitive impairment (Baudry et al., 2012; Simmons et al., 2009). In addition, beyond direct effects of ampakines on excitatory transmission, these compounds also up-regulate the neuronal expression of BDNF (Lauterborn et al., 2000; Rex et al., 2006; Simmons et al., 2011; Simmons et al., 2009), a neurotrophin which has been shown to support neuronal survival and differentiation in brain (Conner et al., 1998), and is critical for LTP and learning (Lynch et al., 2014). Importantly, periodic dosing with ampakines is sufficient to elevate BDNF protein levels in hippocampus and neocortex that can be maintained for days (Lauterborn et al., 2009; Lauterborn et al., 2003; Simmons et al., 2011). It is the dual action of ampakines, both the immediate effects on AMPA receptor currents and the enduring increases in BDNF protein levels well beyond drug half-life, which make these compounds particularly intriguing for use as long-term therapeutics for maintaining neuronal health and function.

Recent work has begun to address the question of whether long-term ampakine treatment could be beneficial by assessing if this treatment regimen

offsets the deleterious effects of brain aging in hippocampus (Lauterborn et al., 2016). In these studies, 10-month old middle-aged rats were treated with the ampakine CX929 (5 mg/kg in 10% honey in water) or vehicle orally on a 5 day-on / 2 day-off schedule for three months and housed in an enriched environment during this period. The enriched housing bin was multi-tiered and contained a nest box, bedding, running wheel, chewable items, and novelty items that were changed weekly. Enrichment was given to both vehicle and ampakine treated animals to avoid possible negative effects of impoverished living associated with standard housing, and to test the effects of the compounds in a situation that is closer to what humans experience daily (i.e., environmental novelty and complexity, physical activity).

Effects of CX929 treatment on behavior were particularly striking, with the ampakine improving both long-term memory and self-organizing behavior. For these studies an unsupervised learning paradigm was used in which animals were allowed 30 min to freely explore a large arena that was divided into “rooms” containing unique objects and had an attached home box, and their forays beginning from the home box through arena space were analyzed; this task is self-directed, non-reinforced. Middle-aged rats receiving ampakine or vehicle were initially tested in the apparatus beginning 5 weeks following the initiation of drug treatment to assess changes in their behavior, and then reassessed 4, 7, and 14 days later to evaluate long-term memory of the complex environment; testing was prior to the daily CX929 treatment to preclude circulating drug effects. For both groups of rats, the average numbers of forays in the apparatus were similar on the first day of testing. On subsequent test days the ampakine treated rats exhibited a marked reduction in total number of forays, whereas the vehicle group did not show this pattern and numbers of forays remained high even with the additional experience. A potential confound to these findings could be if the CX929 had affected arousal, but measures of distance travelled during explorations were not different between drug and vehicle treated groups suggesting little to no effect on arousal. Likewise, ampakine treated rats did not exhibit anxiety related behaviors such as preference for darken spaces or preference for being near walls as opposed to open spaces in the arena; both measures were equivalent between ampakine and vehicle treated groups. The results suggest that the change in exploration across days for the CX929 group reflected enhanced learning during the initial session that did not occur in the vehicle treated group. Next, it was evaluated whether there were differences in the

movement patterns between the two groups of rats within the arena using a Markov sequence analysis; using this technique, predictions errors were calculated for an animal's location at different times in the future based on probabilities from its own past behavior for single transitions between sites within the arena (van der Heijden et al., 1990). These analyses revealed that the prediction errors for ampakine treated rats were significantly less than vehicle treated rats across the testing days, indicating that CX929 treatment helped to organize the exploratory behavior of the middle-aged rats into predictable patterns. Finally, consistent with the improvements in behavior, there were also marked improvements in hippocampal CA1 LTP and a restoration of neuronal cytoarchitecture, including increased dendritic branching and spine growth, in the CX929-treated rats.

The collective findings suggest that ampakine treatment may be useful for restoring neuronal structure and function, and improving spatial working memory that declines with aging (Lester et al., 2017). Importantly though, the results also demonstrate that the drugs are well-tolerated for several months and the positive effects last at least through the period of treatment in otherwise “normal”, albeit middle-aged animals. Thus, the groundwork is now set for similar types of preclinical studies in young animals to test the utility of long-term nootropic treatment combined with environmental enrichment for a wide-range of neurodevelopmental disorders.

Targeting the Ras-ERK pathway for improving cognitive functions

Ras-ERK signaling activation in the adult mammalian brain is a necessary step to establish both long-term plasticity and long-term memories (such as hippocampus dependent spatial reference memory and context fear conditioning), as conclusively demonstrated in a number of electrophysiological and behavioral studies (Davis and Laroche, 2006; Thomas and Huganir, 2004). The Ras-ERK pathway is engaged by several classes of neurotransmitter receptors and tyrosine kinase receptors, such the BDNF receptor TrkB, to regulate changes in gene expression and protein content (Figure 3). Thus, there are several potential routes whereby this signaling pathway can be modulated, to either increase or decrease its activation, including factors that influence BDNF levels and TrkB signaling or directly affect downstream kinase function.

Work of the last two decades indicates that aberrant Ras-ERK signaling in the brain may lead to forms of ID, suggesting that inappropriate signaling in the CNS has

a detrimental effect on a wide variety of human tests on associative learning and spatial and non-spatial learning and memory (Borrie et al., 2017; Fasano and Brambilla, 2011). For instance, gain of function germline mutations upstream in the ERK pathway, including oncogenic variants of the RAS genes and deficiency in neurofibromin, the product of the neurofibromatosis type 1 (NF1) gene, can lead to a plethora of neurodevelopmental disorders collectively indicated as RASopathies (Ehninger et al., 2008; Rauen, 2013; Tidyman and Rauen, 2009). These syndromic disorders include NF1 (neurofribromin gene), Noonan syndrome (NS, mainly PTPN11, SOS1 and KRAS genes), Costello syndrome (CS, HRAS gene), cardio-facio-cutaneous syndrome (CFC, mainly BRAF, KRAS and MEK1/2 genes), and Legius syndrome (LS, SPRED1 gene) (Rauen, 2013). While RASopathies are heterogeneous, they are characterized by a series of common manifestations including cardiac and cutaneous defects, craniofacial dysmorphism, and increased probability of developing benign tumors. Moreover, the majority of these disorders share a variable degree of ID, from mild to severe (San Martin and Pagani, 2014). In addition, loss of function mutations in the SYNGAP1 gene, coding for a brain specific Ras-GAP, have been associated to sporadic, non-syndromic ID forms in approximately 4% of screened cases (Hamdan et al., 2011; Hamdan et al., 2009; Krepischi et al., 2010).

A major turn in our understanding of the neural mechanisms associated to RASopathies and other Ras-ERK dependent ID forms came from recent evidence in rodent models, strongly supporting the notion that mental dysfunction may be caused by an imbalance in excitation/inhibition in the brain (Costa-Mattioli, 2014; Costa et al., 2002; Cui et al., 2008; Fasano and Brambilla, 2011; Papale et al., 2017). On one side, in mouse models of both mild (e.g. NF1, LS) (Costa et al., 2002; Cui et al., 2008) and more severe forms of ID such as Noonan Syndrome $KRAS^{G12V}$ (Fasano and Brambilla, 2011; Papale et al., 2017) behavioral impairments such as episodic memory in the novel object recognition (NOR) task, reference and working memory in the 8-arm radial maze and T-maze and hippocampus dependent associative learning are linked to an increase in GABA inhibition; for Noonan Syndrome in humans, strong activating mutations in KRAS are predictive of an ID phenotype (Carta et al., 2006; Niihori et al., 2006; Schubbert et al., 2006; Stark et al., 2012; Zenker et al., 2007). On the contrary, other mutations associated to milder forms of Noonan Syndrome (Ptpn11-SHP2) (Lee et al., 2014) and SYNGAP1

associated ID (Aceti et al., 2015; Clement et al., 2012; Clement et al., 2013; Ozkan et al., 2014) manifested enhanced excitatory activity. The exact cause of such opposing alterations in the activity of either excitatory or inhibitory neurons is essentially unknown. Moreover, while in some mouse models of these disorders, and in a subset of NF1 patients, treatments with Ras-ERK inhibitors in the adult stage may temporarily ameliorate the cognitive symptoms- such as hippocampus and non-hippocampus dependent forms of associative learning- (Ahmed et al., 2010; Cui et al., 2008; Lee et al., 2014; Li et al., 2005; Mainberger et al., 2013), in other cases it remains unclear whether cellular changes (i.e. synaptic maturation) occurring during post-natal development become essentially irreversible in the adult and may require earlier interventions (Clement et al., 2012; Papale et al., 2017).

Understanding the cellular mechanisms affected by specific mutations in the Ras-ERK pathway could play a crucial role in developing stratified/personalized clinical interventions. As our working model for effects of environmental enrichment indicates, the discriminant factor for a successful therapy is the severity of the pathological state which is directly related to the gene mutation found in the patient to be treated. However, unlike environmental enrichment, a pharmacological approach can be highly selective and targeted based on the cellular pathways involved. Moreover, such an approach clearly has advantages for potentially reducing side effects and resulting in greater gain of function. An additional advantage of targeting directly the Ras-ERK pathway is that such an approach could also ameliorate non-cognitive, peripheral deficits, as recently described (Hernandez-Porras et al., 2014).

Direct tests of Ras-ERK inhibitors in the conditional $KRAS^{G12V}$ mouse model of Noonan Syndrome have been conducted with an effort in treating the cellular phenotypes (i.e. GABAergic synaptogenesis) (Papale et al., 2017; Papale et al., 2016). Importantly though, the pharmacological interventions were only successful when given during early postnatal development, presumably coinciding with the developmental window in which Ras-ERK activity is still high and inhibitory synapses are completing their maturation. By contrast, treatments in the adult were not effective, probably due to the GABA synaptogenetic process already being completed, and relatively lower ERK signaling, by this point.

Recently, two drugs affecting the Ras-ERK cascade were developed and validated, the small molecule MEK inhibitor PD325901 and the cell permeable

peptides (CPP) RB1/RB3 was recently reported (Papale et al., 2016). These two drug classes have been tested in the conditional $KRAS^{G12V}$ model and are also very efficient in blocking cocaine mediated behavioral responses in a mouse model of drug addiction (Papale et al., 2017; Papale et al., 2016). PD325901 is particularly promising in that it is the only clinically relevant MEK inhibitor currently available that passes through the blood brain barrier and it has been tested in several clinical trials for cancer (NCT00147550, NCT00174369, NCT02297802, NCT01347866, NCT02022982, NCT02039336, NCT02510001 NCT020096471). However, PD325901, similarly to other MEK inhibitors, is a rather toxic compound and may not be ideal for prolonged symptomatic treatments, especially in children and teens. An alternative would be to clinically develop cell permeable peptides that have been suggested to be potentially more tolerable, possibly because their IC50 is more in the micromolar rather than nanomolar range (Papale et al., 2017; Papale et al., 2016).

A major central point that should be taken into account for devising an effective treatment of RASopathies with Ras-ERK inhibitors is the severity of the mutation involved and the corresponding temporal profile of ERK activation. Recent work has clearly pointed to the hypothesis that more severe mutations (e.g. KRAS) may lead to accelerated phenotypes, at least in the brain, with a therapeutic window shifted to the juvenile state. Late interventions for severe forms of RASopathies may not work simply because the Ras-ERK pathway becomes normalized. On the other hand, milder phenotypes like those observed in NF1 patients may instead result in incomplete penetrance and a wider temporal intervention window, thus allowing for a treatment also at the adult stage. In addition to those differences, which should be considered during patient recruitment and trial design, it is also relevant to highlight the fact that while an early intervention in severe forms of RASopathies may lead to a permanent “cure” it is possible that a late intervention might only result in symptomatic amelioration.

Altogether the evidence leads us to believe that approaches based on Ras-ERK inhibition may not be only viable for RASopathies but also for other forms of ID and ASD. More specifically, MAPK3, the gene coding for ERK1, lies in recurrent copy number variants (CNVs) at chromosome 16p11.2 (deletions more frequent than duplications, altogether around 1-3 cases in 10,000 people in the general population) which have been associated with ASD, ID and other neurodevelopmental disorders

including schizophrenia, whilst the ERK2 (MAPK1) gene lies within a second recurrent CNV associated with learning disabilities and schizophrenia at chromosome 22q11.2. Importantly, while deletions and duplications at the 16p11.2 locus span many genes, studies integrating common genetic associations and expression data, known as transcriptome wide association (TWAS), have highlighted a wider role for MAPK3 also in non CNV carriers. Specifically, and consistent with duplication of MAPK3 found in 16p11.2 increasing liability to schizophrenia, there is genome-wide significant evidence for an association between increased brain expression of MAPK3 and schizophrenia (Gusev et al., 2018).

Chromosome 16p11.2 CNV contains at least 27 genes, making it a formidable task to devise an effective stratified therapy. However, it has been previously shown that in a mouse model of the 16p11.2 chromosomal deletion, ERK activity is enhanced (Pucilowska et al., 2015). This observation is in line with a model of regulation of ERK signaling which supports a distinct role of ERK1 and ERK2 kinases in governing overall ERK signaling. Whereas ERK2 kinase is the main transducer of downstream signal, ERK1 plays a role of fine negative modulator. This is corroborated by the evidence that a decrease in ERK1/ERK2 ratio enhances while the opposite attenuates global ERK signaling, with corresponding alterations in physiological and behavioral responses (Indrigo et al., 2010; Mazzucchelli et al., 2002; Vantaggiato et al., 2006). Consistent with this view, our recent work in the above-mentioned mouse model of the 16p11.2 deletion showed that treatment with selective ERK pathway inhibitors during gestation can permanently rescue anatomical and behavioural phenotypes such as episodic-like memory (in the NOR test), and hippocampus dependent spatial reference and working memory (Davis, 1995; Pucilowska et al., 2018; Pucilowska et al., 2015). Furthermore, treatment in adult mice also showed amelioration of the above behavioral symptoms (Pucilowska et al., 2018). This strongly supports the view that gene dosage impacting on the ERK pathway contributes to phenotype of the 16p11.2 CNV and that compounds targeting the ERK pathway may represent an effective therapeutic intervention. Finally, elevated ERK activity has been reported for the Fragile X mouse mutant, the Fmr1 KO (Wang et al., 2012), and the Ras-ERK inhibitor lovastatin has been shown to improve behavior in children and adults with FXS (Caku et al., 2014). It is thus possible to envision that pharmacological treatment with a Ras-ERK inhibitor may be useful for amelioration of attention and working memory deficits, and a rescue of the

molecular and cellular phenotypes, in a number of developmental disorders with disparate etiology.

VI. Future Directions

Therapies that combine environmental enrichment with those that promote neuronal activity and signaling (e.g. Ras-ERK pathway selective) and/or facilitate BDNF (e.g., ampakines), could prove to be a particularly useful approach for improving learning and memory in multiple forms of cognitive impairment including those that emerge during early development and with aging. Further work is needed though to understand the degree to which improvements can be made on dendritic spine defects and for cognitive/behavioral impairments across different disorders or conditions of impairment, and treatment regiments that are most effective. To this point, work with ampakines suggests that daily treatment is tolerable and effective for improving outcomes in adult animals, although further work is needed to assess if similar treatments are also beneficial in pre-weanling animals and without unwanted effects on the developing nervous system. As BDNF expression (Friedman et al., 1991; Timmusk and Metsis, 1994) and activation of the key dendritic spine actin regulatory protein cofilin (Lauterborn et al., 2017) both emerge in rat brain by the second postnatal week, this period may represent an optimal point at which the initiation of treatments could be most effective for modulating glutamatergic synapses and promoting neurotrophin expression during development. Importantly, work with Ras-ERK compounds in one mutant model of ID suggests early interventions are likely critical for correcting deficits associated with cognitive impairment that emerge in development (Papale et al., 2017; Papale et al., 2016; Ruiz-DeDiego et al., 2018). Positive outcomes would further support the idea of early interventions for most individuals with developmental intellectual disabilities to fully correct spine defects by the time they reach adulthood.

An alternative strategy could involve other key components of the downstream TrkB receptor. One of these is the nuclear kinase mitogen- and stress-activated protein kinase 1 (MSK1), which has gained considerable interest in the field of cognitive enhancement. MSK1 has been identified as a link between cell-surface neurotransmitter receptors and the gene expression necessary for long-term memory (Choi et al., 2017; Karelina et al., 2012; Karelina et al., 2015). MSK1 exerts its physiological effects by coupling the activation of BDNF receptors to the

regulation of transcription via the phosphorylation of CREB (Daumas et al., 2017; Hunter et al., 2017), and due to its position within the nucleus, could be a more precise target for a putative nootropic. MSK1's role is central for homeostasis in response to environmental changes and is highly involved in environmental-induced synaptic transmission effects via its action on immediate early gene activity-regulated cytoskeletal protein Arc/Arg3.1 (Correa et al., 2012; Daumas et al., 2017; Hunter et al., 2017).

For the adult brain, aging, and age-related cognitive disorders (e.g., Alzheimer's disease), future work is also needed to address when is the most optimal time to begin treatments that are the most beneficial. The work described here for one pharmacological approach indicates that beginning treatment during middle age does have profound effects at least through a relative short period in the animal's life thereafter. But whether these changes can be sustained and tolerated through long-term aging is not known. Additional work is needed to evaluate these questions for the effectiveness of both environmental enrichment and nootropics.

Finally, for studies aimed at evaluating drugs and other therapies including environmental enrichment on cognition, several other important factors need to be considered. The first is the behavioral approaches that are used in preclinical research for higher-order cognitive domains such as executive functions and working memory, and how predictive they are for humans. Second, is the choice of enrichment for the animal (e.g., opportunity for intense physical activity; animals socially housed; novelty introduced on a regular basis) sufficient and complex enough for inducing changes in the brain. This is an important consideration for studies using mutant mice, as mild forms of enrichment may not be sufficient to (i) see a positive effect on phenotype or, conversely, (ii) reveal the full phenotypic capacity that is needed for then evaluating the effectiveness of therapeutic compounds.

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Figure Captions

Figure 1. Higher cognitive functions are influenced by the underlying mnemonic, emotional and health status of the subject in exam.

Figure 2. Proposed model for how wild type (WT) and ID mouse models differ in response to the level of environmental enrichment, leading to genotype differences in neuronal effects (e.g., neuronal cytoarchitecture, synaptic plasticity) and cognitive behavior. Under this model, greater enrichment results in larger phenotypic differences between WT and ID mouse models, primarily due to greater responsivity under the WT condition. In contrast, environmental deprivation would be expected to negatively influence both genotypes, potentially leading to a floor effect. As discussed more fully in the main text, differences in enrichment, especially between laboratories, can lead to the possibility of inconsistent behavioral tests results as often observed and reported in the literature. Deprived environment: e.g., social isolation (1 mice / cage) and no other enrichment; Impoverished environment: e.g., 2 mice/cage without cardboard tubes nor toys; Standard environment: e.g., 4 mice/cage cardboard tubes, toys and tunnels; Environmental enrichment: e.g., 8 mice / rat sized cage, running wheel, cardboard tubes, toys, tunnels.

Figure 3. The Ras-ERK pathway implements neuronal adaptations such as protein synthesis and modulation of synaptic connections in response to environmental changes and can be the target for several types of nootropics. The schematic depicts some key components of the Ras-ERK pathway. A variety of mechanisms can activate Ras proteins such as glutamate NMDA receptors and calcium signaling, G-protein-coupled receptors (e.g., dopamine receptor D1R) or tyrosine kinase receptors (TRK). Membrane signals converge toward Ras exchange factors RAS-GFR, SOS and Ras-GRP that activate RAS proteins; the docking protein GRB2 and adapter protein SHC facilitate receptor activation of Ras. In the cytoplasm, the protein kinase cascade is then initiated by sequential activation of RAF, MEK and MAPKs of the ERK family to elicit nuclear transcription (red arrows); note that ERK can also affect protein synthesis via other routes as well (e.g. S6K). Once translocated into the nucleus, MAPKs can phosphorylate transcription factors such as CREB that leads to expression of immediate early genes (IEGs) such as c-Fos.

Some of these products are themselves transcription factors and might induce late response genes (LRGs). It has been proposed that MSK1 and ERK 1/2 might have opposing effects on the transcription factor CREB and Histone H3 phosphorylation leading to further fine tuning of gene expression. Protein kinase A (PKA) and C (PKC) can activate this cascade in a fashion that is independent from Ras, thus providing an additional level of regulation. As shown (blue asterisks) several classes of nootropics can target key points that either initiate the pathway (e.g., ampakine-induced increases in the neurotrophin BDNF and enhanced TRK signalling) or are in the pathway (MEK inhibitors) to regulate Ras-ERK signalling and downstream protein synthesis; up- or down-regulation of the pathway would depend on the individual intellectual disability defect. Appropriate levels of protein synthesis are needed for long-term modulation of synaptic contacts and for memory formation and consolidation.

Table 1. Commonly-used tasks to investigate higher-order cognitive domains in humans versus similar type studies in rodents. We acknowledge that these tests might not be equivalent between the two species in probing the specific domains.

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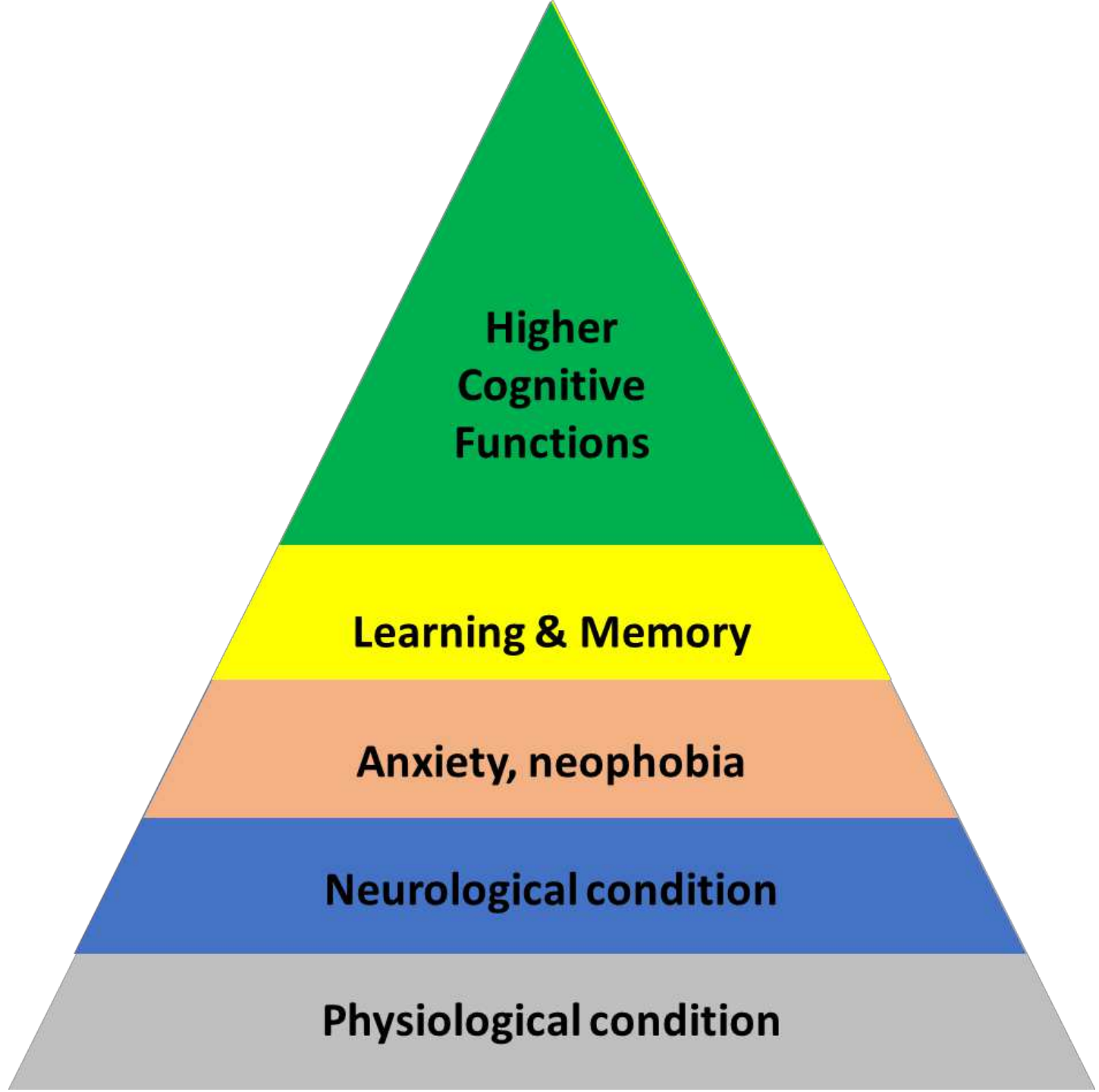
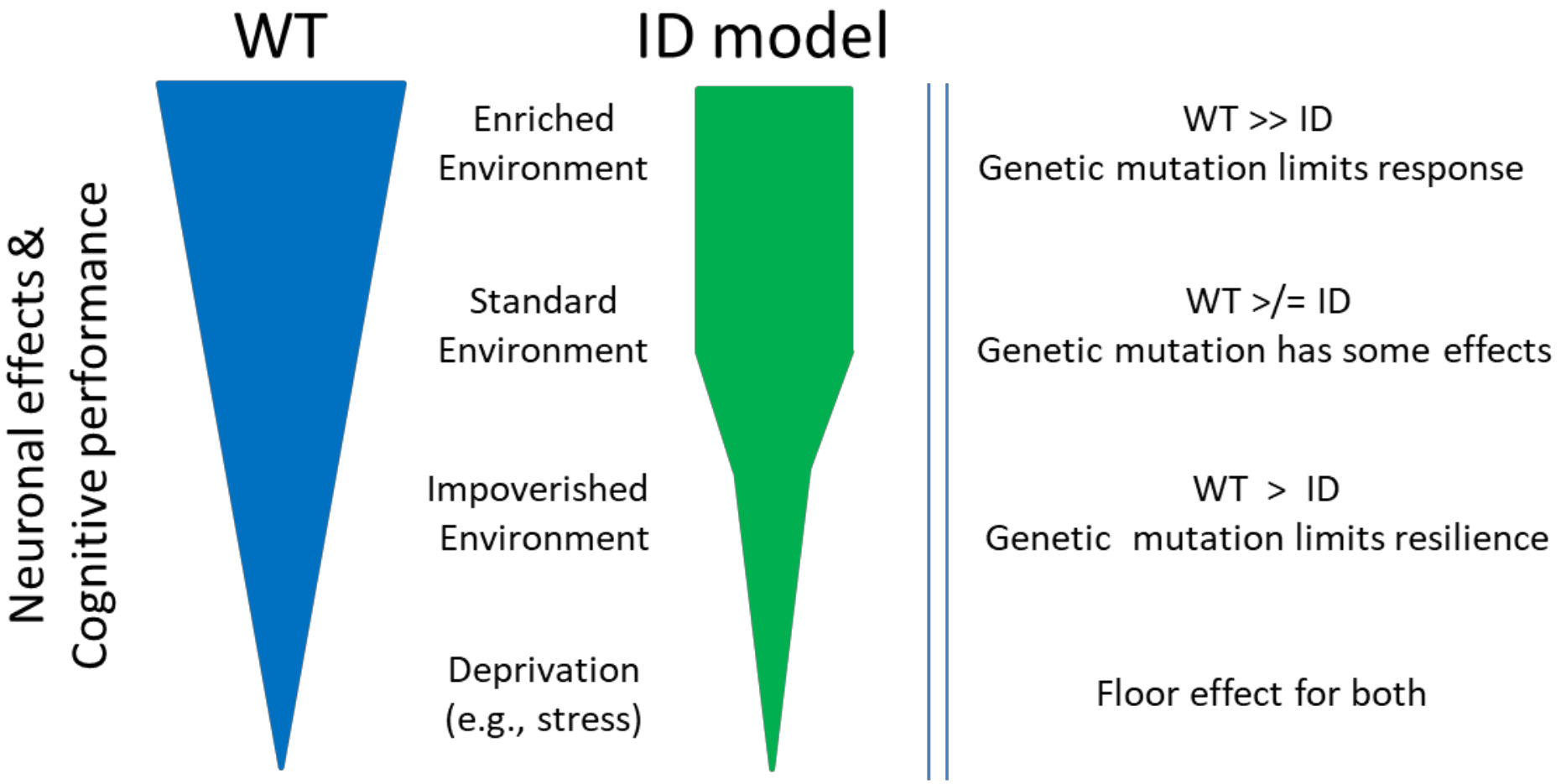

Higher
Cognitive
Functions
Learning & Memory
Anxiety, neophobia
Neurological condition
Physiological condition


WT
ID model
Neuronal effects &
Cognitive performance
Enriched
Environment
Standard
Environment
Impoverished
Environment
Deprivation
(e.g., stress)
WT >> ID
Genetic mutation limits response
WT >/= ID
Genetic mutation has some effects
WT > ID
Genetic mutation limits resilience
Floor effect for both

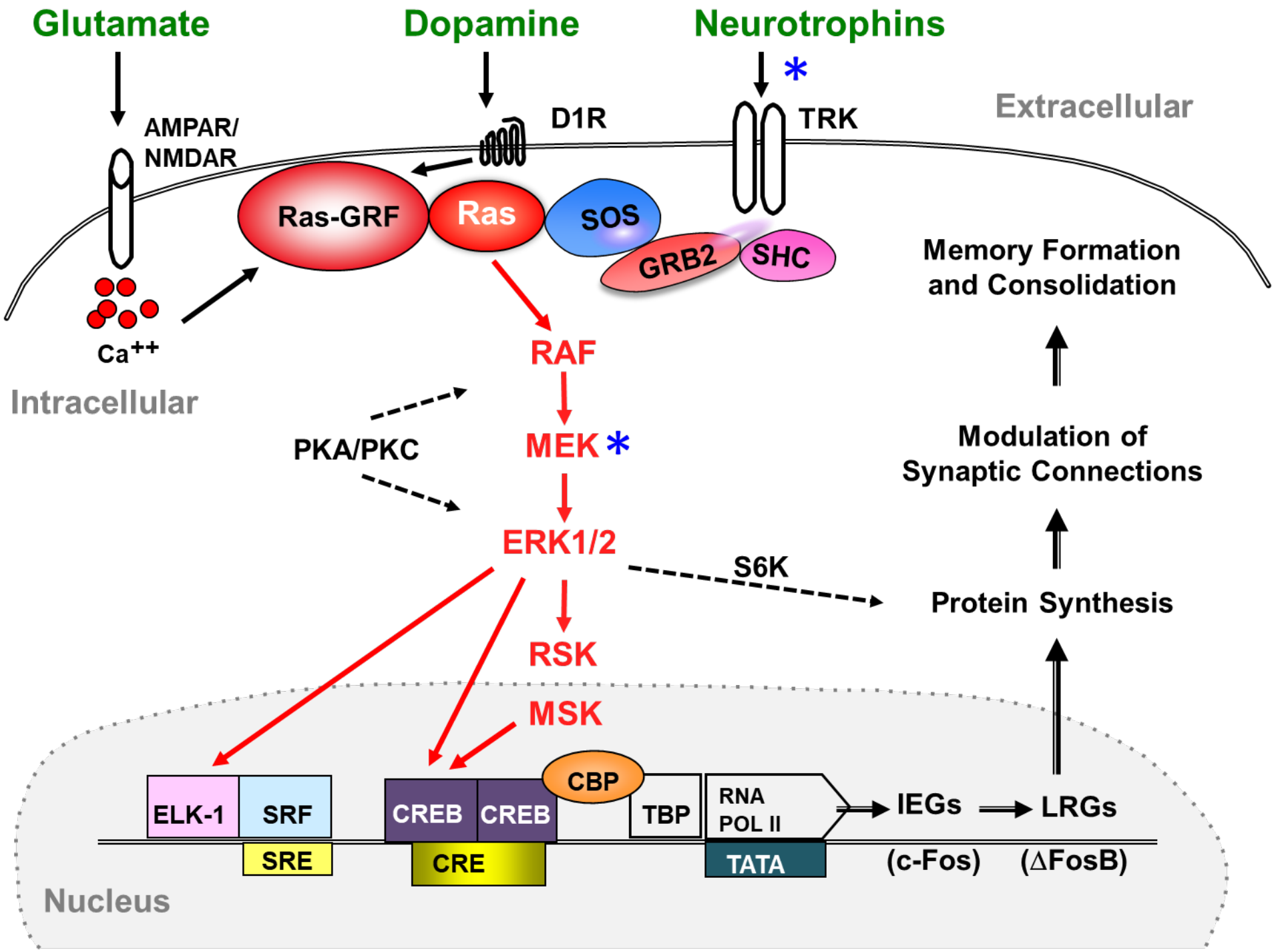

Glutamate
Dopamine
Neurotrophins
*
AMPAR/
NMDAR
D1R
TRK
Extracellular
Ras-GRF
Ras
SOS
GRB2
SHC
Memory Formation
and Consolidation
Ca++
Intracellular
RAF
PKA/PKC
MEK *
Modulation of
Synaptic Connections
ERK1/2
S6K
Protein Synthesis
RSK
MSK
CBP
ELK-1
SRF
CREB
CREB
TBP
RNA
POL II
IEGs
LRGs
SRE
CRE
TATA
(c-Fos)
(ΔFosB)
Nucleus

Table 1

Widely-used Human tasks	***Widely-used Rodent tasks***
Cognitive Control	
1. Wisconsin Card Sorting Task (WCST) 2. "intra- and extra-dimensional attentional set-shifting" of the Cambridge Neuropsychological Test Automated Battery (CANTAB)	1. Attentional set-shifting "digging" task 2. Stuck in set
Working Memory	
1. n-back task 2. Spatial delayed response task 3. List sorting	1. T-maze discrete paired-trial variable-delay alternation task 2. Spontaneous alternation 3. 8-arm radial maze "delayed non-match to sample" or ''win-shift'' task 4. 8-arm maze "random foraging task" 5. Odor span tasks 6. Delayed matching and delay non-matching to sample position operant conditioning tasks 7. Simultaneous stimulus processing
Episodic Memory	
1. Interview or self-report 2. "what, when, where" tasks	1. Novel object recognition 2. Object location task 3. Object in place 4. Temporal order discrimination
Attention	
1. Continuous Performance Test (CPT) 2. CPT-Identical Pairs (CPT-IP) 3. A-X CPT versions 4. Spatial Attentional Resource Allocation	1. 5-Choice Serial Reaction Time Task (5-CSRTT) 2. Distractor Condition Sustained Attention Task (dSAT)

Task (SARAT)	
Social Cognition	
1. Emotion recognition tasks 2. Self-report inventories	1. Observations of maternal/parental behaviors, colony formation/hierarchy, peer interactions, nest-building, sleeping/resting in group huddles 2. Observations of social interactions between two unfamiliar animals, including sniffing, following, climbing on, ultrasonic vocalizations, allogrooming, fighting, and sexual behavior 3. Three-chamber social approach task 4. “habituation/dishabituation” paradigm 5. Place conditioning – social stimuli 6. Appetitive conditioning – social stimuli