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REVIEW ARTICLE

Positive Emotional Learning Induces Resilience to Depression: A Role for NMDA Receptor-mediated Synaptic Plasticity

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Abstract: ***Background***: Positive emotions have been shown to induce resilience to depression and anxiety in humans, as well as increase cognitive abilities (learning, memory and problem solving) and improve overall health. In rats, frequency modulated 50-kHz ultrasonic vocalizations (Hedonic 50-kHz USVs) reflect a positive affective state and are best elicited by rough-and-tumble play.

Methods: The effect of positive affect induced by rough-and tumble play was examined on models of depression and learning and memory. The molecular and pharmacological basis of play induced positive affect was also examined.

Results: Rough-and-tumble play induced Hedonic 50-kHz USVs, lead to resilience to depression and anxiety, and facilitation of learning and memory. These effects are mediated, in part, by increased NMDAR expression and activation in the medial prefrontal cortex.

Conclusions: We hypothesize that positive affect induces resilience to depression by facilitating NMDAR-dependent synaptic plasticity in the medial prefrontal cortex. Targeting MPFC synaptic plasticity may lead to novel treatments for depression.

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Keywords: Positive affect, rat, resilience, rough-and-tumble play, stress, ultrasonic vocalizations.

1. MEASURING POSITIVE AFFECTIVE STATES IN HUMANS

The highest levels of positive affect occur when socializing with friends or ones romantic partner [1, 2]. As such, social stimuli that elicit positive affect are widely used in experimental studies (*i.e.*, positive social feedback/ reciprocity, giving a small gift, or even just watching a video tape eliciting positive affective state); for recent summaries of research, see [3]. Experimentally induced positive affective states increase sociability, optimism, and openness to new experiences [4, 5].

Positive affect associated with subjective well-being and consummatory pleasures are functionally distinct. Positive affect elicited experimentally by hedonic food or regulatory stimuli (*e.g.* thermal) show that the function of these sensory pleasures is primarily to maintain homeostasis. For example, the pleasure derived from a warm shower in cold individual would be directly proportional to the ability of the stimulus to return the body to homeostasis [6]. This affectively driven change in the value of sensations is associated with a return to homeostasis, and is called sensory alliesthesia [6, 7]. In a sense, the social-emotionally driven positive feelings, from play to maternal care and enthusiasms are in a different category, and probably more relevant for regulating joy and depression, and overall subjective well-being.

2. POSITIVE AFFECT AND RESILIENCE TO DEPRESSION

Longitudinal studies of positive affective states show that positive affect induces resilience to depression and anxiety and increases overall health with a concomitant decrease in mortality [4]. The beneficial effects of positive affective states appear to be mediated through the strengthening of diverse neuronal processes that overall amount to increased resilience. Resilience is defined as continued global functioning despite the presence of stressors. For example, a resilient individual is less likely to develop depression or anxiety following a major life stressor [8, 9]. Positive affect precedes the health benefits of positive affect in longitudinal studies, suggesting a causal relationship [4]. Activities that

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promote health, such as regular exercise, reduce depression [10]. Like exercise, only sustained positive affect induces resilience. Short-term positive or negative life events have little long-term beneficial effects [11]. In contrast, low levels of positive affect are associated with the development of anxiety disorders, depression, and global health problems [4]. Increasing positive affect *via* therapeutic interventions reduces levels of depression and anxiety in adults [12, 13] and promote feeling of "a meaningful life, optimism, and goal orientation" in children [14].

3. NEUROBIOLOGY OF POSITIVE AFFECT IN HUMANS

The mesolimbic dopamine system is implicated in the generation of positive affect. Brain imaging studies using a wide variety of positive affect inducing stimuli (*i.e.* hedonic memory recall, hedonic music, anticipation of a monetary reward, and orgasm) all activates parts of the mesolimbic dopamine system including the ventral tegmental area, nucleus accumbens, as well as medial and/or orbitofrontal cortices [15-19]. Functional studies show that the hedonic effects of intravenous amphetamine are positively associated with nucleus accumbens dopamine binding [20, 21], whereas electrical stimulation of the accumbens increases both positive affect and Duchenne laughter [22-24]. Long-term studies of electrical stimulation of the medial forebrain bundle, recently characterized in humans [25], and this stimulation induces a robust and long lasting antidepressant effect [26-28].

4. POSITIVE AFFECT IN LABORATORY ANIMALS

Measuring positive affect in animals requires that the following homologies with human positive affect are present. (1) Positive affect is primarily measured by self-report and facial/vocal expressions such as felt- or Duchenne-smiling [29]. In animals studies, only facial / vocal displays can be quantified, and the predicted change in approach behavior observed. (2) Positive affect is best elicited by friendly social interaction (including play), exercise and food and is decreased by aversive stimuli [1, 2, 30]. Therefore, in animals these same rewards should increase and aversive stimuli should decrease the facial/vocal display. (3) What is known about the neurobiology and pharmacology of human positive affect should translate to the animal model.

Positive affect in animals can be modeled by the frequency modulated 50-kHz ultrasonic vocalizations (50-kHz USVs; discussed below), and hedonic taste reactivity [31]. The first has also been validated with Deep Brain Stimulation (DBS) [32, 33], which has been validation in human DBS studies [23].

The goal of this line of research is to develop a simple vocal measure of positive affect, such as how squeaking or screaming expresses pain in rats. However, to our knowledge these responses have not been formally validated with DBS, even though it is well known that the most sensitive brain regions such as the dorsal periaqueductal gray, are consistently aversive. Thus, it is to be expected that the ability of DBS of brain regions such as the periaqueductal gray that produce separation calls in the young of many animals [34] and 22-kHz type "complaints" in adult rats, tends to promote depressive responses in rats [35] . In sum, research involving rats expressing frequency modulated 50-kHz USVs has been proposed as potential non-semantic 'self-report' of positive affective [32, 36-38], while those at the 22-kHz level reflect negative affective states [35, 36, 38].

4.1. 50 kHz Vocalizations in Rats as Measures of Positive Affect

These frequency modulated 50-kHz USVs reflect a positive affective state in rats (Table **1**). A wide range of hedonic stimuli (social, food, drugs of abuse), increase calling rate [39-42], whereas aversive stimuli uniformly decrease call rate [39, 42, 43]. Calling rate is positively correlated to the rewarding value of a wide range of hedonic stimuli [33, 42]. Additionally, alternative hypotheses are not supported by the available experimental data. Lastly, this measure readily discriminates resilient and non-resilient rats at the behavioral, pharmacological and molecular levels [44-46].

5. MEASURING RESILIENCE TO DEPRESSION IN ANIMALS

Animal models of resilience typically examine a subset of animals that do not show depressive-like response to stress or use enrichment methods to prevent stress-induced depressive-like behaviors. Both repeated social defeat stress and chronic unpredictable stress have been used to induce a depressive-like state. Chronic unpredictable stress (CUS) induces a long-lasting and robust depressive-like phenotype that models clinical features of depression in humans and has been well characterized at the behavioral, physiological, cellular, and molecular levels. The depressive-like phenotype elicited by CUS is responsive to chronic, but not acute, antidepressant treatment [47, 48]. Moreover, CUS causes atrophy of neurons in rodent prefrontal cortex and hippocampus [49, 50], which might lead to a reduction in the volume of those regions similar to the decreased volume reported in brain imaging studies of human Major Depressive Disorder (MDD) patients [51, 52]. Repeated social defeat stress also has been shown to induce a robust depressive-like state in rodents. In a similar manner as CUS, the depressive-like effects of social defeat at the behavioral level are ameliorated by repeated but not acute SSRI treatment, and social defeat decreases spine density in the medial prefrontal cortex (MPFC) and hippocampus [53, 54].

Table 1. Evidence that frequency modulated 50-kHz ultrasonic vocalizations (hedonic 50-kHz USVs) reflect a positive affective state in rats. Reviewed in [32]

1. Positive affective stimuli selectively increase rates of hedonic 50-kHz USVs
2. Negative affective stimuli decrease rates of hedonic 50-kHz USVs
3. Stimuli that elicit hedonic 50-kHz USVs are rewarding
4. The neural circuitry of hedonic USVs 50-kHz is similar to human positive affect.
5. Alternative hypothesis are not supported.

Environmental enrichment has been used to induce resilience to depression in these stress models. Environmental enrichment has been shown to robustly increase positive affect as measured by Hedonic 50-kHz USVs as well as saccharin preference [55, 56]. In a similar manner as humans, environmental enrichment induced positive affect leads to resilience to depression in rat exposed to chronic stress [55, 57].

6. POSITIVE EMOTIONAL LEARNING

Positive emotional learning (PEL) leads to resilience to depression (Fig. **2**). One of the key symptoms of depression is anhedonia as well as negative cognitive bias especially in social interactions [58]. Depressed patients typically avoid social interactions that are rewarding to non-depressed people and report ambiguous social interactions as negative [59]. In contrast, rewarding social interactions and social support clearly confers resilience to depression [9]. Interventions that increase the rewarding aspects of social interactions alleviate symptoms of depression in depressed patients.

In rats, the rewarding value of hedonic social interactions (*i.e.* rough-and-tumble play) is rapidly learned across time and exposure [60], serving as a positive incentive for social learning [34]. Within a single 3 min rough-and-tumble play session, the amount of positive affect is increased across time, as measured by rates of Hedonic 50-kHz USVs. In specific, the PEL test measures the acquisition of hedonic/aversive ultrasonic vocalizations (USVs) to a social stimulus (heterospecific rough-and-tumble play) during a single 3 min test session. This assay captures both the anhedonic symptoms (as measured by decreases in hedonic 50-kHz USVs in chronically stressed rats) as well as the symptoms of increased negative affect (as measured by increased aversive 22-kHz USVs in chronically stressed rats) of depression, and importantly the rate at which the animals learn these responses. Antidepressants have been shown to decrease rates of the aversive rat ultrasonic vocalizations [61]. In addition, animals that readily learn to show a hedonic response to rough-and-tumble play also show a positive cognitive bias in operant tasks [62], which has been shown to be a hallmark of resilience to depression in humans [63].

Therefore, PEL represents a core shift in affective set point / bias that is critical for resilience to depression. Consistent with the human literature, hedonic rough and tumble play in rats alleviates the depressive-like, anxiogenic-like and cognitive impairing effects of chronic stress (Fig. **2**).

7. SELECTIVE BREEDING FOR DIFFERENTIAL RATES OF 50 KHZ AND 22 KHZ USVS AS A MODEL FOR RESILIENCE / SUSCEPTIBILITY TO DEPRESSION

Across 18 generations, rats were selectively bred to exhibit high, random, or low rates of 50-kHz USVs in response to heterospecific rough-and-tumble play [39, 64]. Across a wide variety of behavioral tests, high line rats showed lower rates of anxiety-like behavior as well as a concomitant decrease in aversive 20-kHz USVs during play. In contrast, low line rats showed increased anxiety-like behavior in these same tests as well as a concomitant increases in aversive 20-kHz USVs during play. These behavioral phenotypes were stable from adolescence into adulthood (3 months). Biochemical studies also confirmed these phenotypic differences. High line rats showed elevated levels of Met-enkephalin-like immunoreactivity in the ventral tegmental area [72], and microinjections of the μ-opiate agonist DAMGO into this same brain regions increases rates of 50-kHz USVs [66]. Low Line animals showed increased levels of cholecystokinin (CCK) -like immunoreactivity in the posterior neocortex. Social defeat also elevates levels of CCK in the posterior cortex and is positively correlated with 20-kHz calling rates [65], and CCK administration also increases 20-kHz USVs calling rates [66].

8. HEDONIC 50-KHZ USVs AS A TOOL TO UNCOVER THE MOLECULAR SUBSTRATE OF POSITIVE AFFECT

Genes associated with positive affective states can be uncovered by examining transcripts that are upregulated by hedonic play, but not aversive social defeat [60, 67, 68]. Using an in-house fabricated focused microarray platform, that is able to detect families of genes that are specifically upregulated following hedonic rough-and-tumble play when using appropriate bioinformatics tools. These mRNA changes are corroborated by quantitative qrtPCR and quantitative protein assays (Radioimmunoassay, ELISA, Western blots). Using this approach, both the insulin like growth factor I (IGFI) and the NMDA NR2B receptor subunit are specifically upregulated by hedonic rough-and-tumble play and are therefore associated with positive affect.

Function studies with IGFI and NR2B demonstrated that they play a regulatory role in positive affective states [60, 67]. IGFI (intracerebroventricular) increased hedonic USVs in an IGFI receptor (IGFIR) dependent manner, whereas intracerebroventricular injections of an IGFIR specific siRNA reduced 50-kHz USVs calling rates. As shown in Fig. **1**, intravenous dosing with the NMDAR glycine site functional partial agonist, GLYX-13 (rapastinel; 3 mg/kg) increases, whereas intraperitoneal dosing with the NMDA receptor antagonist, MK-801 (0.25 mg/kg), decreases rates of 50-kHz USVs. Bilateral medial prefrontal cortex injections of rapastinel (1 μg/side) also increased rates of 50-kHz USVs whereas dorsal lateral control injections did not.

The modulation of glutamatergic transmission has become a major target in the development of antidepressants for biogenic-amine antidepressant resistant patients [69-71]. The NMDAR antagonists CP-101,606 and ketamine produces robust antidepressant effects in treatment-resistant depressed patients [72, 73]. Ketamine also produces a robust antidepressant effect in patients with treatment-resistant bipolar disorder [73]. However, these drugs produced clinically unacceptable dissociative side effects at therapeutic doses. The efficacy in these studies was significant, showing a >50% response rate in resistant subjects along with both a fast onset of action and long duration of effect (7 or more days following a single dose). Like ketamine, rapastinel produces a rapid-acting and long-

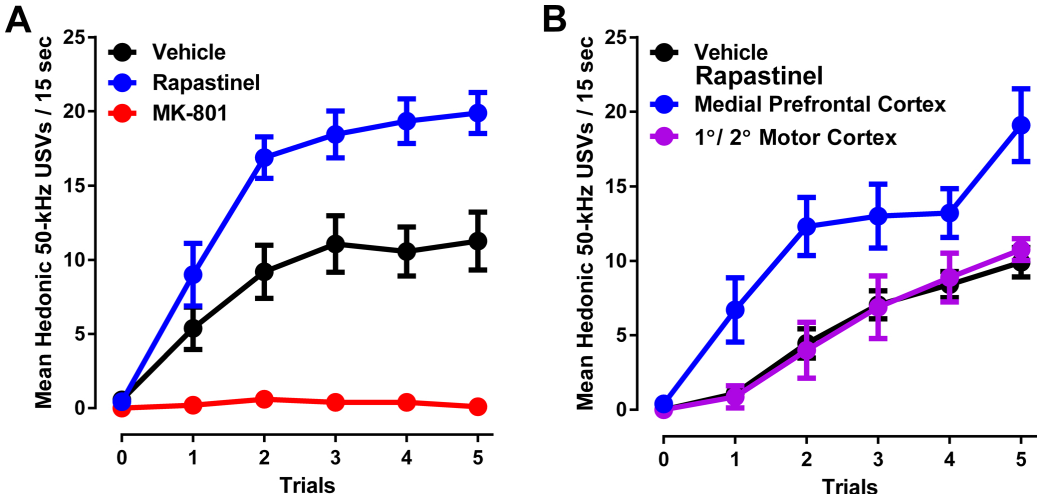

Fig. (1). Positive Emotional Learning is a NMDAR-dependent, medial prefrontal cortex localized learning task. (**A**) Adult male rats were pretreated with a single dose of the NMDAR glycine site functional partial agonist rapastinel (TPPT-NH2; 3 mg/kg IV) or the NMDAR channel blocker MK-801 (0.25 mg/kg IP) or sterile saline vehicle (0.9%, 1 ml/kg IV or IP) or (B) medial prefrontal cortex or somatosensory cortex control injections of rapastinel (1 µg/side) or sterile saline vehicle (0.9%, 0.5 µl into the MPFC or M1/M2 cortex) and were tested 20 min post-dosing. The Positive emotional learning test consisted of a single 3 min of heterospecific rough-and-tumble play (dubbed "tickling") consisting of alternating 15 s blocks of play and 15 s of no-stimulation. Rates of hedonic 50-kHz USVs during the no-stimulation intervals, which serves as conditioned stimulus that predicts further play was quantified for each trial. N = 8-20 per group. Data adapted from [60].

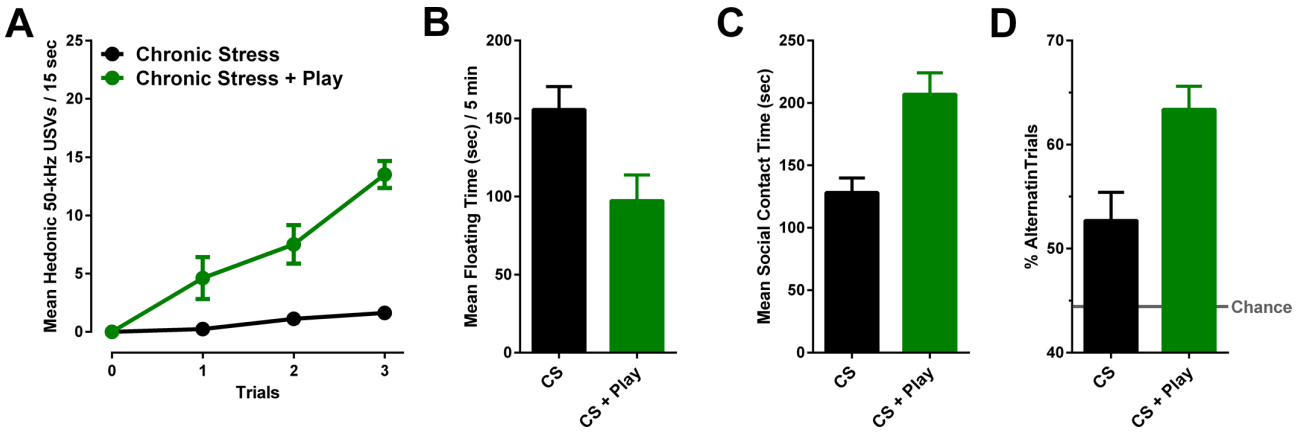

Fig. (2). Hedonic rough-and-tumble play facilitates positive emotional learning and induces resilience to depression in rats. Rats received 30 min play session (play group) or 30 min alone in a conspecific's homecage (no play group) twice per day during the peak developmental play period (PND 22-36), and all animals received 2 hrs of restraint stress once a day from 60 to 74 days of age. At 1-7 days after restraint stress, animals were tested in the (**A**) positive emotional learning test, (**B**) Porsolt test of depression, (**C**) File test of anxiety, or (**D**) the spontaneous alternation plus maze test of learning and memory. N = 8 per group. Data adapted from [88].

lasting robust antidepressant-like effect in multiple rat models of depression and in humans [74-76]. However, unlike ketamine or CP-101,606, rapastinel shows no sedative or dissociative side effects clinically or in pre-clinical models [74, 76].

9. NMDA RECEPTORS AND SYNAPTIC PLASTICITY

NMDA receptors are critical for the induction of some forms of LTP in MPFC and hippocampal slices, as well as for learning and long-term memory *in vivo* that measure MPFC or hippocampal dependent tasks [77]. The induction, but not long-term maintenance, of LTP at some (but not all) excitatory synapses in hippocampal and MPFC slices is blocked by the NMDA glutamate receptor antagonist APV, and by NMDAR channel blockers such as MK-801 and ketamine [78, 79]. In addition, NMDA receptor activation promotes LTP [80]. However, once LTP has been induced by events including the insertion of AMPA receptors into synapses in a protein synthesis dependent manner, the increased synaptic efficacy that is the expression of LTP is not blocked by NMDAR antagonists [77]. *In vivo,* learning acquisition and long-term memory formation are also blocked by NMDAR antagonists, including positive emotional learning [60, 79]. Thus, the formation of the most well studied form of LTP is triggered by NMDAR activation and maintained by AMPA receptor synthesis, cell surface trafficking, and activation [77, 78].

In rat hippocampal slices, rapastinel has been shown to: 1) preferentially enhance conductance of NR2B-containing NMDARs at rat Schaffer collateral-CA1 synapses (Zhang *et al.*,

2008), and 2) enhance the magnitude of LTP of synaptic transmission while simultaneously reducing that of long-term depression (LTD) at the same synapses, which differentiates rapastinel from other NMDAR modulators such as D-cycloserine [80, 81].

In whole animal studies, rapastinel has been shown to: 1) enhance performance in a variety of hippocampal-dependent learning tasks, including trace eyeblink conditioning and the Morris water maze, in both young adult and learning-impaired aged rats [81]; 2) markedly reduce CA1 pyramidal neuronal cell death 24 hours after bilateral carotid occlusion in Mongolian gerbils when administered up to 5 hours after induction of occlusion ischemia [82]; 3) produce analgesic effects in the rat formalin and Bennett models of sustained pain [83], and 4) produce an antidepressant-like effect in Porsolt, learned helplessness, and novelty induced hypophagia tests in non-chronically stressed rats, without ketamine-like dissociative, addictive or sedative side effects [74, 76]. Finally, rapastinel facilitates positive emotional learning (PEL) and produces antidepressant-like effects when injected directly into the infralimbic or prelimbic MPFC, but not when injected into dorsal-lateral control sites (primary/secondary motor cortex; see [60, 74]).

10. METAPLASTICITY AND RESILIENCE TO DEPRESSION

A NMDAR dependent LTP-like metaplasticity process in the MPFC, whereby the magnitude of LTP elicited by a stimulus can be regulated, appears to dynamically change the threshold for positive affect to induce resilience to depression. Environmental enrichment increases positive affect as indexed by hedonic 50-kHz USVs [56], induces resilience to depression, and facilitates metaplasticity, making LTP more likely [84], whereas prodepressive stressors suppress LTP [85]. Deep brain stimulation in both rats and humans induces positive affect and produces an antidepressant-like response by activating the descending MPFC-MFB-raphe positive affect circuit [27, 33, 86]. Metaplasticity in this circuit can lower the threshold to induce positive affect and hence lead to an antidepressant response.

Targeting metaplasticity may be a viable therapeutic target for depression. In rats, both rapastinel and IGFI have been shown to increase metaplasticity and make LTP easier to induce, and both show robust antidepressant activity in rats and humans [67, 74, 75, 87]. In addition, ECT and SSRIs induce similar metaplasticity and are antidepressants [85].

CONCLUSION

Rat 50-kHz USVs can be used to model positive affect and resilience to depression, and behavioral, biochemical, and molecular studies using this model have identified NMDAR dependent synaptic plasticity in the MPFC as being critical for positive affect induced resilience to depression. The form of metaplasticity in the MPFC appears to mediate positive emotional learning which is critical for the development of resilience to depression. Targeting MPFC metaplasticity may be a useful therapeutic target for the development of novel antidepressants.

CONFLICT OF INTEREST

P.K. Stanton and J.S. Burgdorf are consultants for Naurex, Inc., and have received financial compensation and stock. EM. Colechio is an employe of Naurex, Inc., and has received financial compensation and stock.

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