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Still controversial issues on assessing anhedonia in experimental modeling of depression

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Dear Editor,

In response to Berrio, J.P., Hestehave, S. & Kalliokoski, O. Reliability of sucrose preference testing following short or no food and water deprivation—a Systematic Review and Meta-Analysis of rat models of chronic unpredictable stress. *Transl Psychiatry* **14**, 39 (2024). https://doi.org/10.1038/s41398-024-02742-0

In a recent issue of Translational Psychiatry, Berrio et al. [1], reported their meta-analysis regarding the appropriateness of using sucrose preference test (SPT) as a tool to evaluate depressive-like behavior and anhedonia; specifically, the traditional practice to use food or water deprivation before the test to incentivize sweet consumption has represented a significant confounding factor, since (i) the sweet taste per se is rewarding for rodents, (ii) the consumption of a sweet solution under a condition of deprivation may be driven by non-hedonic factors, like the metabolic state of the animal [1]. In the same vein, Primo et al. [2], performed a systematic review of SPT protocols, showing a high degree of variability between studies in the procedures used, particularly in relation to the conditions of habituation, to the presence and duration of food/water deprivation, to the duration of testing, to caloric content of the reward; moreover, different hedonic responses were found between males and females and across strains and species [2]. SPT appears therefore very sensitive to multiple variables and manipulations and the lack of a standard, optimized protocol, also shared by the scientific community, has produced heterogenous and sometimes contradictory results in preclinical research, affecting enormously the internal validity of SPT and the readout provided [1, 2]. In addition, two different research groups using a similar approach aimed to analyze drinking microstructure during the SPT [3, 4] have demonstrated that many behavioral subcomponents are associated with the expression of sucrose preference and, again, have raised the question whether the reduced sucrose preference is indicative of anhedonia [3].

Not aside from the methodological considerations, very critical is whether the changes in sucrose preference really reflect an anhedonic/ depressive state and may therefore be translated in humans. In support of this analysis, several points should be considered. First, in rodents exposed to chronic stress that elicits a depressive phenotype, some authors set arbitrarily a cut-off in the percentage of sucrose preference to define anhedonia and remarkably, the reduced percentage of sucrose consumed after stress exposure not always is an expression of anhedonia, but is dependent on subcomponents like deficits in learning, motivation and memory, as elegantly demonstrated by [3]. For example, the switching of the position of sucrose and water bottles during the SPT increases the contribution of learning processes and therefore the behavioral outcome may not reflect only the hedonic response [3]. Second, changes in sucrose preference are not associated with changes in the threshold during intracranial self-stimulation [5]. Third, the impairment in consummatory pleasure in depression is still controversial (no alteration in sweet taste was found in anhedonic patients [6]) and depressed patients experience a higher decreased motivation to approach secondary reinforcing stimuli such as monetary or social reinforcer rather than primary naturalistic stimuli like food [7].

From its original definition as "diminished interest or pleasure in response to stimuli previously perceived as rewarding", the concept of anhedonia has been revisited and now it is considered a multi-dimensional construct, distinguishing between consummatory, motivational and decisional anhedonia [8]. Thus, it is unlikely that a single test such as SPT may capture the full spectrum of anhedonia and different approaches may be necessary to characterize reward responsiveness. Several translational procedures have been developed to assess specifically the different aspects of reward processing. For example, motivational anhedonia can be evaluated by the Progressive Ratio task (PR), that defines the maximum effort a subject is willing to exert by progressively increasing the number of responses required for reward, or by effort-related choice (also called Effort Expenditure for Rewards in humans), which are based on the evaluation of effort costs and expected rewards [7, 9, 10]. Both tasks are applicable to humans [11, 12] and animal models, as reviewed in [13, 14], rendering them very appropriate tools for translational studies. Typically, animals press a lever or make a nose-poke to receive the reinforcer (palatable food, e.g., sucrose pellets) while humans usually respond on a keyboard or use a joystick to obtain a monetary reward. When the response requirements are reached, the reward is delivered; when the response requirements become too high, stop responding occurs (breaking point). In PR studies, lower breaking point values, reduced response rates and less sensitivity to rewards have been observed in depressed patients [11, 12], along with deficits in saliency attribution to reward attainment (rather than reduced disposition to expend effort to purse potential rewards, [15]). In addition, PR and effort related tasks are very useful to quantify reward and to dissect the directional and activational/arousal components of motivation (the directional component allows to select the behavior producing the optimal outcome while the activational component allows to properly initiate and maintain the actions), also in relation to their sensitivity to outcome devaluation [10]. Another critical question concerns the role played by other subcomponents of reward processing in the development of anhedonia, particularly those involving aspects of learning and cognition and that are crucial to adjust the behavior as a function of previous rewarding experiences. Probabilistic reward tasks, based on the ability to discriminate two stimuli ("rich" or "lean") to obtain the reinforcer, are for example valuable tools to measure reward learning [14]. Several lines of research demonstrated that both depressed subjects and rats exposed to stress showed a blunted response bias and reduced hedonic capacity [14, 16], suggesting how the deficit in the ability to integrate rewarding experiences over time may in turn contribute to the decline in motivation. However, when confronting human and animal tasks, it is also important to point out that the motivational incentives are classically different (monetary rewards for

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human subjects and primary rewards for animals) and may be mapped in different brain regions; therefore, they may elicit a distinctive pattern of neuronal activation, limiting the translational value of procedures based on learning and motivation.

As previously discussed, anhedonia is not a unitary construct and has been considered a transdiagnostic phenotype of the Research Domain Criteria (RDoC), that focuses on identifying core brain-behavior systems and biological processes underlying psychopathological conditions, with the intent to transcend the classical categorical diagnostic criteria based on symptoms. The analysis of RDoC have emphasized that deficits in the subcomponents of anhedonia, such as reward responsiveness, reward learning and approach motivation, are associated with deficits in the meso-cortico-limbic dopaminergic transmission. Neuroimaging studies have consistently shown blunted responses in Nucleus Accumbens in MDD subjects compared to healthy controls during reward processing, despite an unexpected hyper-response in other regions like orbitofrontal cortex has been emerging [17]. Parallelly in rats, anhedonic states associated with lower breaking points for sucrose pellets, showed also reduced levels of dopamine in the NAc and blunted dopaminergic response to positive cues, while pharmacological treatments that restore the dopaminergic response to the consumption of sucrose also reinstate sucrose operant behavior [13, 18]. Notably, the activation of meso-cortico-limbic dopaminergic pathways is critical to assign an incentive value to reward-associated cues, which is crucial for the pursuit and attainment of goals. On this ground, breaking point may reflect a measure of the construct of the Positive Valence System within the RDoC system.

Thus, the use of the appropriate test to investigate anhedonia should be considered particularly relevant in experimental modeling of depression since we still must answer many important questions regarding the neurobiology of depression, why standard treatments for depression do little to alleviate anhedonia, and critically, no US Food and Drug Administration-approved treatment currently exists specifically for anhedonia.

Simona Scheggi [1]✉
[1]*Department of Molecular and Developmental Medicine, University of Siena, Siena, Italy.* ✉*email: simona.scheggi@unisi.it*

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AUTHOR CONTRIBUTIONS

All contributions were from the single author.

COMPETING INTERESTS

The author declares no competing interests.

ADDITIONAL INFORMATION

Correspondence and requests for materials should be addressed to Simona Scheggi.

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