Effects of ALTO-203 on positive emotion and reward processing: methods and supporting data for an ongoing phase 2 proof-of-concept study

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1. Background

- Extensive data suggest that a reduction in reward system dopaminergic signaling is a crucial aspect of depression for many patients, yet no treatments specifically target this dysfunction.
- Anhedonia, the lack of pleasure or motivation, may reflect dopaminergic dysfunction
- The Histamine H3 receptor (H3R) is a brain-specific negative regulator of multiple neurotransmitter systems, including dopamine.
- ALTO-203 is a novel H3R inverse agonist shown to increase dopamine release in the nucleus accumbens in rodents, and thus may improve reward sensitivity, motivation and anhedonia in MDD patients.
- In a phase 1 trial, ALTO-203 acutely increased positive subjective emotion measured by the Bond-Lader Visual Analogue Scale (BL-VAS) at a level comparable to modafinil, a drug known to enhance reward system dopamine release and evaluated in the study as an active control arm (along with placebo).
- To examine the clinical and pharmacodynamic effects of ALTO-203 in depression, we have initiated a Phase 2 double-blind Proof-of-Concept (POC) study in patients with Major Depressive Disorder (MDD) exhibiting anhedonia symptoms.

2. ALTO-203 Proof-of-Concept Study

- The ALTO-203 POC study (ongoing) involves a 3-week single dose period, followed by a 4-week daily dose treatment period. Figure 1 outlines the design.
- The powered primary outcome is change in BL-VAS scores compared to placebo in the single-dose period. BL-VAS was chosen as it is sensitive to momentary changes in emotional state, which adaptations of traditional depression scales may not be.
- Additional outcomes include safety, pharmacokinetics, and pharmacodynamic markers associated with mood, cognition, and reward-processing (depression scales will be measured in the multi-dose period as exploratory outcomes)
- The study may also refine dosing strategies and identify pharmacodynamic markers for future patient targeted therapies.

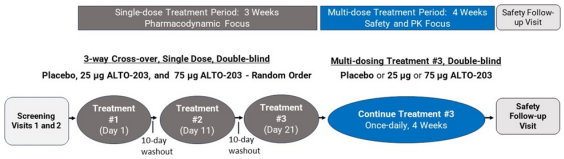

Figure 1. POC study design flowchart. The order of doses received is randomized and in the multi-dose period, whichever dose was given at treatment #3 is continued.

3. Development of Reward Tasks

- While a number of tests of reward processing have been previously established (e.g., PRT [1] and EEfRT [2]), they tend to be lengthy and poorly tolerated by clinical populations. They may also have low test-retest reliability and inconsistent correlations with clinical constructs like anhedonia.
- To more effectively characterize pharmacodynamic changes in the POC study, we developed and validated two computerized tests for different aspects of reward processing and motivation and examined their relationship to anhedonia.
- Effort Tapping (Figure 2) is a free-operant paradigm where participants can earn +10 (low reward) or +100 points (high reward) each time they press a key during periods of 3 to 17 seconds. Akin to findings with apathy [3], we hypothesized that participants with higher anhedonia would show a lower rate of pressing during the low reward (+10) versus high reward condition, indicating greater sensitivity to reward condition.

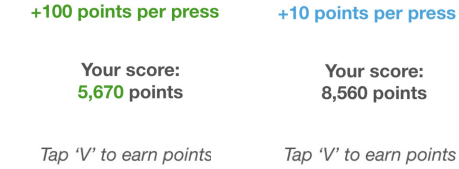

Figure 2. Screenshots for the Effort Tapping task. The left screen shows a trial in the high reward condition and the right screen shows the low reward condition. In each of 3 rounds participants aim to get 20,000 points.

- The Probabilistic Instrumental Learning Task (**PILT**, Figure 3) is an adaptation of a two-armed bandit test that measures the ability to learn arbitrary stimulus-reward probabilistic associations. The task involves multiple rounds with novel stimulus pairs becoming progressively harder to distinguish.
- We used a Rescorla-Wagner Bayesian reinforcement learning model to model behavior in PILT, resulting in an estimate of learning rate (α) and decision noise (β) parameters. We hypothesized that anhedonia would be associated with a lower learning rate and increased decision noise [4].

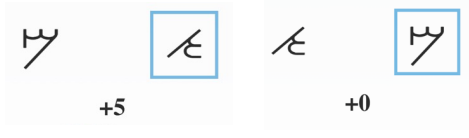

Figure 3. Screenshots for the PILT task. The left screen shows the 'reinforced' symbol being selected. The right screen shows a trial where the 'non-reinforced' symbol is selected. Left/right side presentation is randomized on each trial.

4. Pilot Study for Parallel Forms Reliability

- An online pilot study in 70 participants was run with a two-week follow-up, using parallel forms of each task, entailing randomized durations for high/low reward sequences for Effort Tapping, and alternating symbols and trial sequences for PILT.
- Primary outcome ICC's for tasks were: Effort Tapping high minus low (0.73), PILT decision noise (0.83).

5. Reward Task Validation Methods and Results

Abbreviation	Test Name	Outcome variable
PRT	Probabilistic Reward Task [1]	Response bias ('Log b') towards the (long or short) mouth with higher reward probability across 2 rounds of 100 trials.
EEfRT	Effort Expenditure for Rewards Task [2]	Percentage of 50 administered trials choosing the hard (100 pinky taps) over the easy (30 taps) condition ('EEfRT % hard').
DDT	Delayed Discounting Task	ED50, delay duration at which $10 reward is considered of equal value to $5 now, using five adaptive prompts to determine.
Tapping	Finger Tapping (sensorimotor)	Mean latency for 150 dominant hand index finger keyboard taps.
PHQ-8	Patient Health Questionnaire	Removed the suicidality question from the PHQ-9.
SHAPS	Snaith-Hamilton Pleasure Scale	Anhedonia scores flipped to match the direction of DARS/PVSS.
DARS	Dimensional Anhedonia Rating Scale [5]	Lower scores indicate greater anhedonia.
PVSS	Positive Valence Systems Scale [6]	Lower scores indicate greater anhedonia.
BIS/BAS	Behavioral Inhibition/Activation System [7]	Measures sensitivity to reward (BAS) and punishment (BIS); different subscales interpret sensitivity.

Table 1. Abbreviations and task and questionnaire names and descriptions.

- The new tasks, plus tasks and surveys from Table 1, were obtained for a new online sample of 168 participants aged 18 - 70 years (mean 37.8), 60.1% female.
- The sample was actively enriched for subjects with PHQ-8 above 9, to prevent restriction of range for the key measures of interest, reward sensitivity and anhedonia. Overall distributions were PHQ-8: 8.1 [6.5], SHAPS: 24.6 [6.0].
- To establish convergent validity, new tasks were compared to established tasks.
- **Each of the new tasks showed some significant correlations with established tasks** (Figure 4) – despite the new tasks not using monetary rewards. The Effort Tapping primary outcome 'high minus low' did not correlate.

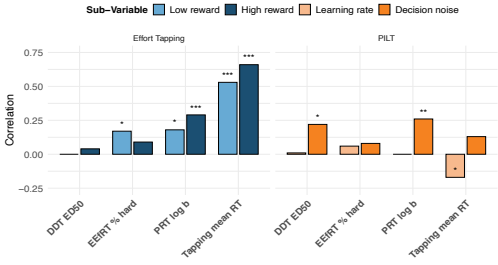

Figure 4. Correlation of features from the Effort Tapping and PILT tasks with key outcome scores from established reward tasks (see Table 1 for abbreviations). Tapping scores flipped for consistent interpretation with other tasks.

Statistical Significance
* p<0.05
** p<0.01
*** p<0.001

- Effort Tapping and PILT, as well as the established tasks, were then correlated with five self-report scales of anhedonia, mood and activation/inhibition (Table 1).
- **Performance in the new reward tasks was significantly correlated with anhedonia, positive emotion, and BIS/BAS measures** (Figure 5).
- Effort Tapping showed a positive correlation between tapping rate differences in high minus low reward conditions and DARS and PVSS, suggesting increased sensitivity to the level of reward in anhedonic subjects.
- The PILT decision noise correlated positively with BIS/BAS Drive and Reward Responsiveness, suggesting higher motivation and reward responsiveness predicts better task performance. Learning rate did not show any associations.

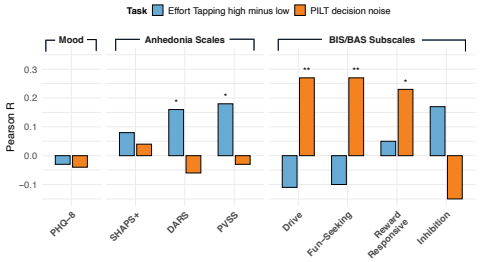

Figure 5. Correlation of Mood, Anhedonia and BIS/BAS scales with *Effort Tapping* high minus low taps, and *PILT* decision noise. See Table 1 for abbreviations for the scales on the x-axis.

Statistical Significance
* p<0.05
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- Participants were asked to rate each task on a visual 5 point scale (pleasantness). **The new tasks were rated as more tolerable than established tasks,** Effort Tapping ($p < .05$, D=0.15) versus EEfRT, and PILT versus PRT ($p < .001$, d=0.6).
- Median time taken for the new tasks was 3.6 minutes and 4 minutes respectively, versus 20.7 minutes and 17.2 minutes for EEfRT and PRT.
- **No correlations with anhedonia were seen for PRT or EEfRT**, suggesting they tap into different aspects of reward and motivation, or that using a monetary incentive (traditional approach) overcame any anhedonic bias in sample of participants that were being paid to do this experiment.

6. Conclusions

- Results from preclinical and early human studies show promising pharmacodynamic effects of ALTO-203 on reward system dopaminergic functioning and analogous subjective emotional responses in humans.
- Two new computerized cognitive tasks measuring reward learning and reward sensitivity show improved test-retest reliability, are shorter and better tolerated, and display evidence of construct and external validity through association with anhedonia, motivation and established reward tasks.

7. References

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