

Translating Animal Models into Clinical Programs: The IRIS Trial for Investigational ML-004 in Autism Spectrum Disorder

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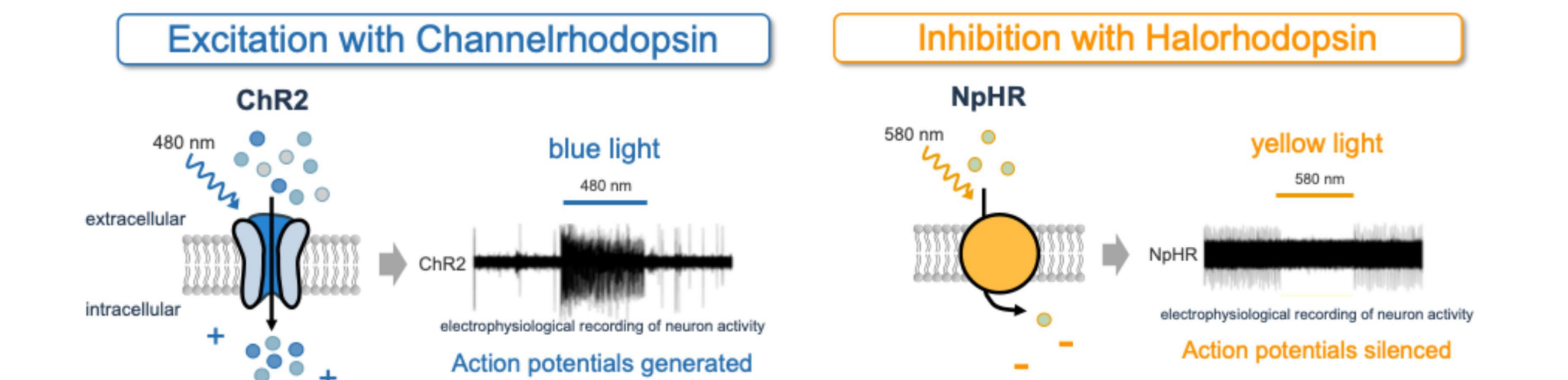
Introduction

Autism Spectrum Disorder (ASD) is a heterogeneous condition affecting complex social behaviors for which there are no existing pharmacologic treatment options. Individuals experience persistent deficits in social communication and social interaction across multiple contexts¹, for example:

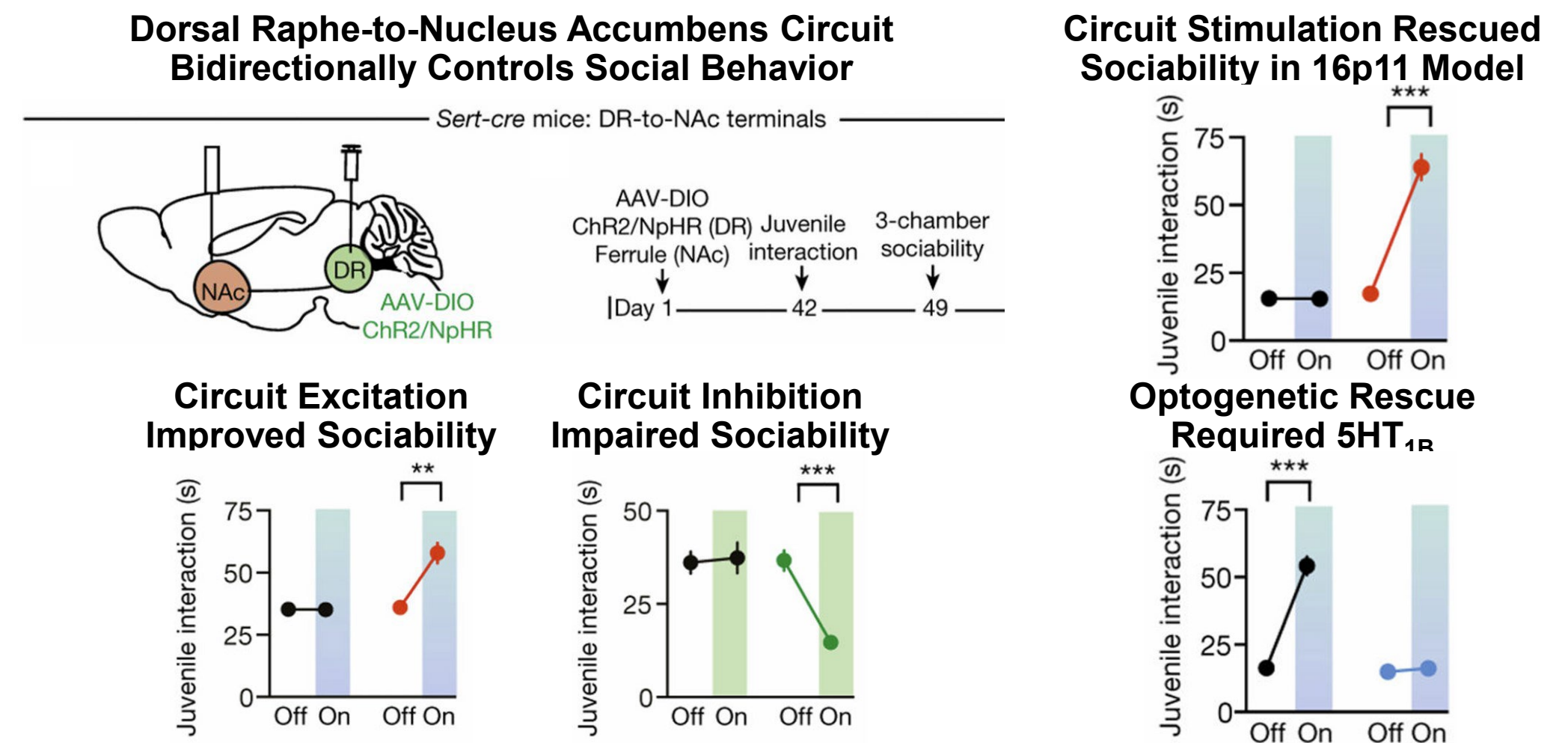
- Abnormal social approach; failure of normal back-and-forth conversation; reduced sharing of interests, emotions, or affect; failure to initiate or respond to social interactions
- Deficits in nonverbal communication behaviors used for social interaction
- Difficulties adjusting behaviors to social contexts, difficulties engaging in play or making friends, absence of interest in peers

Social deficits are challenging to study in preclinical animal models. As a result, they are constrained to measuring constituent behaviors of human social interaction (eg, social preference and aggression). To maximize model utility, MapLight adopted a circuit-based approach to interrogate the function of neural circuitry associated with social behavior and selected a molecule (ML-004) to engage the target (5-HT_{1B}) that modulates this function. An ongoing Phase 2 study of this candidate is designed to evaluate the consequences of circuit modulation in ASD, including an eye tracking measure that may be an indicator of engagement of social preference circuitry.

Optogenetic Identification of the 5-HT_{1B} Target



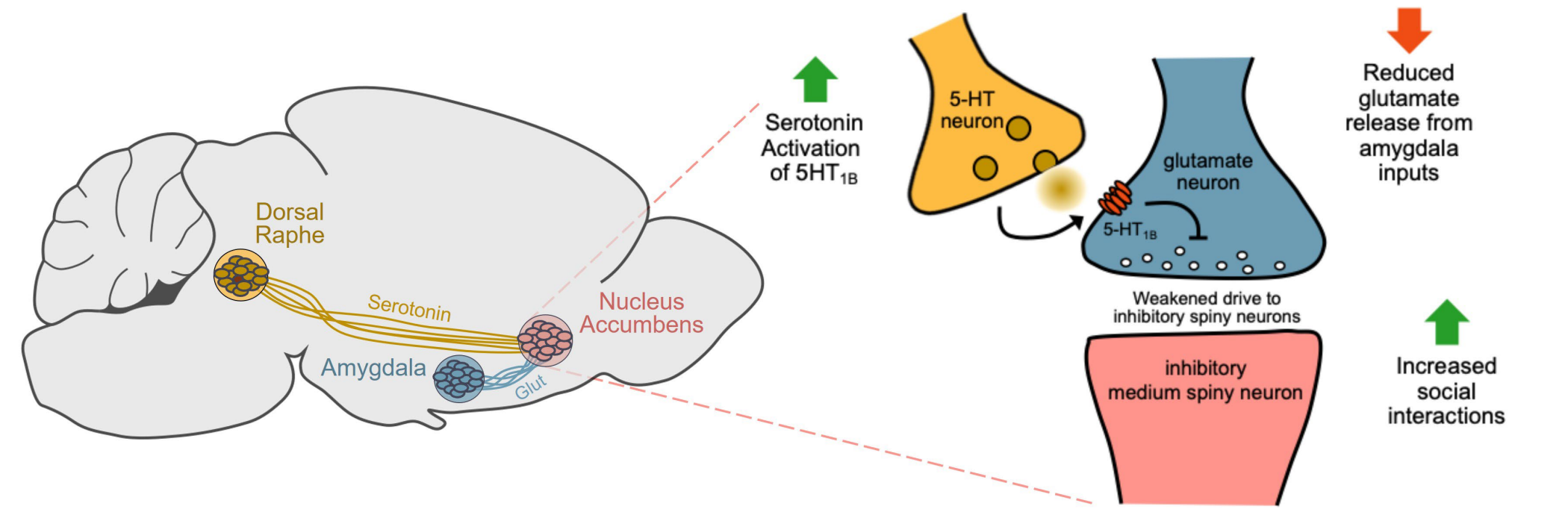
Light-activated opsins can be expressed in genetically defined cell types using viral-mediated gene delivery to enable bidirectional neural circuit control in awake, behaving preclinical animals. Figures adapted from Yizhar et al., 2011² and Gradinaru et al., 2010.³



Preclinical work by MapLight's scientific co-founder demonstrated that optogenetic stimulation and inhibition of the dorsal raphe (DR) to nucleus accumbens (NAc) circuit bidirectionally modulated sociability.⁴ Local NAc infusion of a 5HT_{1B} antagonist (NAS-181) blocked optogenetic rescue of sociability in the 16p11 mouse model of ASD. Figures adapted from Walsh et al., 2018.⁴

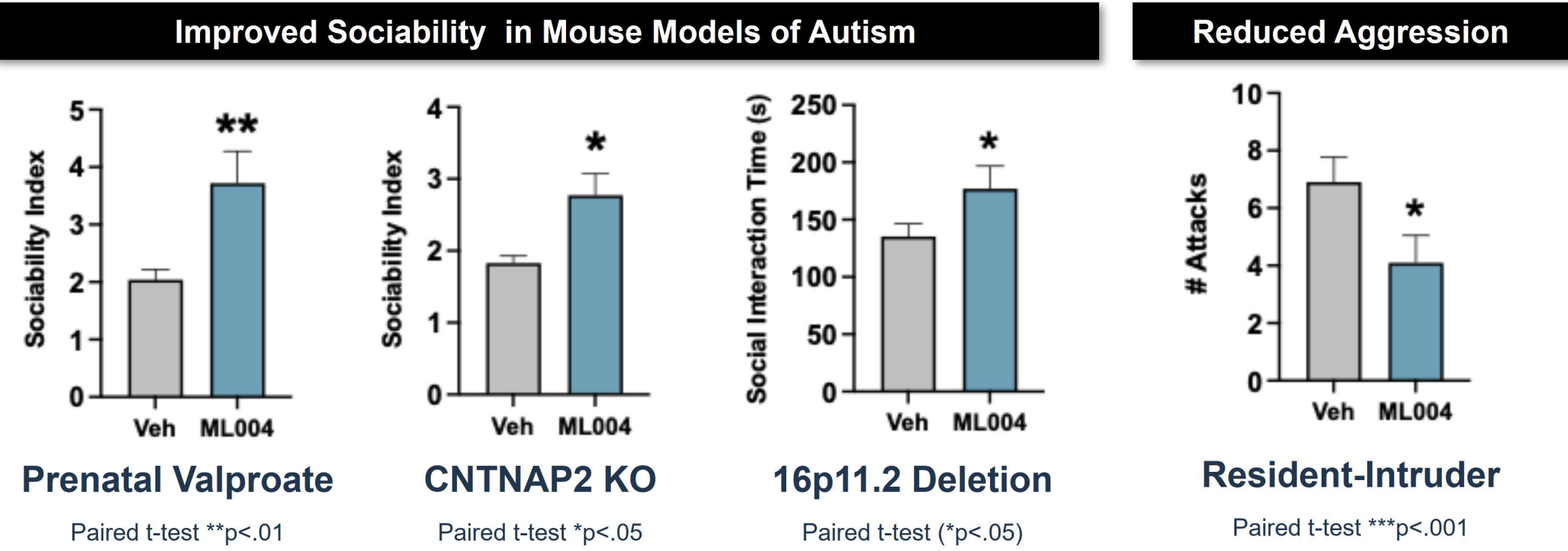
Circuit-Based Approach to Intervention

- We hypothesize that sociability requires activation of 5-HT_{1B} receptors on excitatory glutamatergic amygdala inputs to the nucleus accumbens that modulate glutamate release from the amygdala
- Reduced glutamatergic drive of postsynaptic nucleus accumbens spiny neuron activity increases the reward associated with social interactions to promote sociability



ML-004 Improved Sociability in Mouse Models of Autism and Reduced Aggression

ML-004 is an investigational 5-HT_{1B/1D} agonist being evaluated for social communication in a Phase 2 study for ASD. Preclinical data support the potential to address social communication deficits and irritability symptoms.



Preclinical studies demonstrated efficacy for ML-004 to improve social interaction in 3 mouse models of autism (prenatal valproate, CNTNAP2 knock-out, and 16p11.2 deletion). Mice were administered IP with either vehicle or 10 mg/kg ML-004 and then immediately tested for sociability in the 3-chamber interaction test. Aggression was measured using the resident-intruder assay.

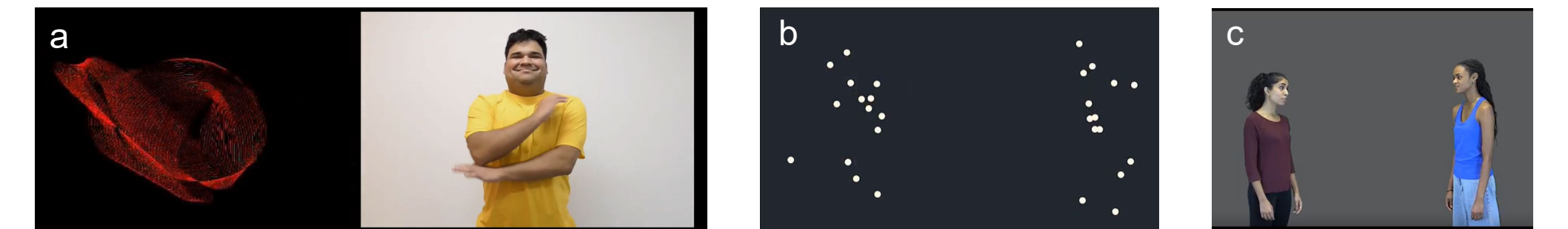
Given these results, MapLight designed a Phase 2 trial to test whether ML-004 could increase sociability in individuals with ASD, including eye tracking as an exploratory measure with translational potential.

References

1. DSM-5
2. Yizhar et al., 2011
3. Gradinaru et al., 2010
4. Walsh et al., 2018
5. Pignatelli & Beyeler, 2020
6. Itier & Batty, 2014
7. Adolphs, Tranel, & Damasio, 1998
8. Stuart et al., 2023

Eye Tracking as a Potential Translational Measure to Monitor Circuit Engagement of ML-004

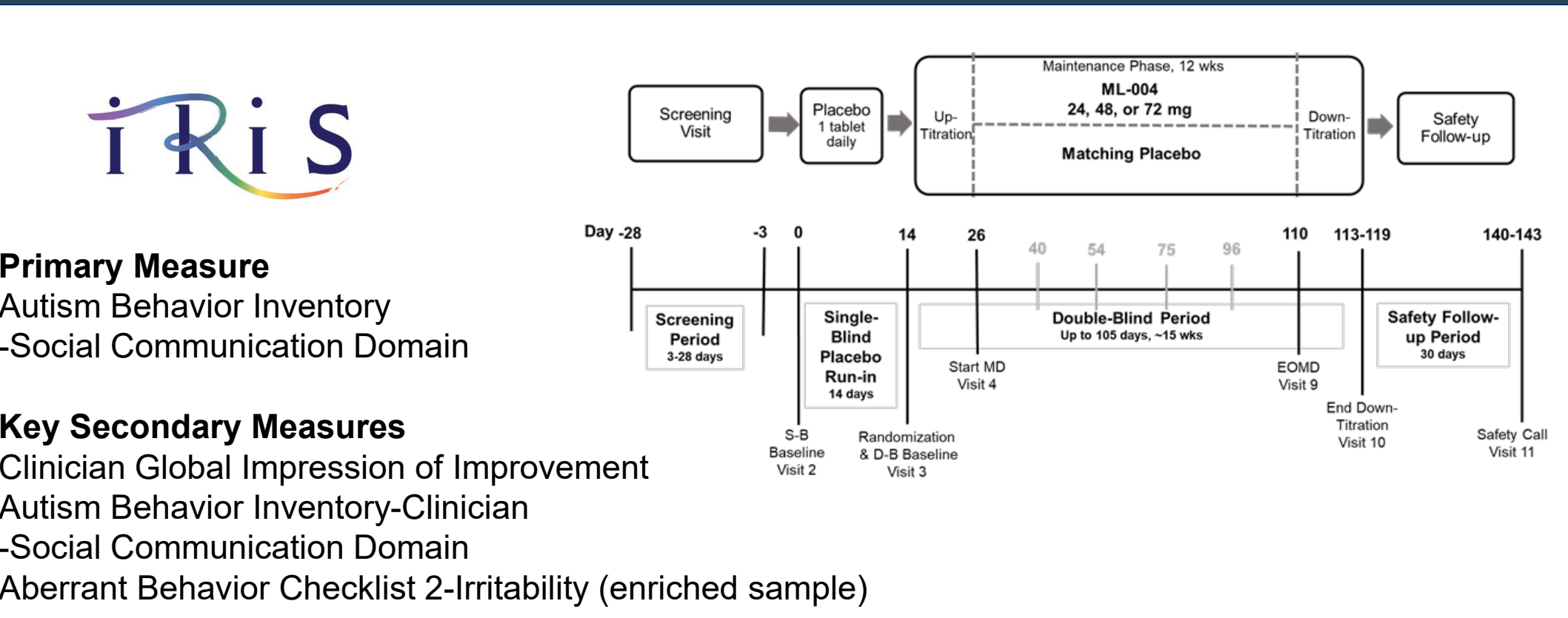
Exploratory Eye Tracking Measure: Proportion of eye gaze time directed at social stimuli versus other stimuli in (a) isolated contexts, (b) biological motion, and (c) conversation following.



Eye tracking engages social preference circuitry that is modulated by the 5-HT_{1B} target

- The amygdala assigns valence to external stimuli mediating approach-avoidance behaviors.⁵ It has also been implicated in social eye gaze control⁶ and social judgment.⁷
- Both amygdala hyperactivation⁸ and reduced eye gaze (especially directed at faces during social interactions) are commonly found in ASD individuals.⁶
- Agonism of the 5-HT_{1B} receptor is predicted to reduce glutamate release from the amygdala into the nucleus accumbens and promote social reward.
- Therefore, eye tracking may be a viable indicator of ML-004 engagement of social preference circuitry.

Ongoing Phase 2 Autism Spectrum Disorder Trial



Summary

- A circuit-based approach to interrogate the function of social behavior circuitry identified a target with potential efficacy to modulate these circuits and the clinical ASD symptoms they mediate.
- ML-004 is an investigational 5-HT_{1B/1D} agonist in Phase 2 testing for social communication deficits in autism with exploratory eye tracking endpoints intended to monitor engagement of social preference circuitry.

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