

Bionomics



BNC210: A Novel Therapeutic in Development for PTSD



CREATING INNOVATIVE THERAPIES
FOR SERIOUS HUMAN DISEASES.

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October 2017

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What is Posttraumatic Stress Disorder?

PTSD is:

- a well defined and accurately diagnosed condition
- a set of reactions that can develop in some people who have experienced a traumatic event which threatened their life or safety, or that of others around them, like combat, a natural disaster, a car accident, or sexual assault.

People with PTSD continue to experience memories and feelings of intense fear, helplessness or horror long after the trauma was experienced.

Diagnosis of PTSD is performed using the Clinician Administered PTSD Scale based on symptom cluster criteria from DSM-5

B. Intrusion symptoms (1/5) (e.g., nightmares, flashbacks, intrusive thoughts, and physiological reactions to trauma reminders).

C. Avoidance of stimuli associated with the trauma (1/2) (intentionally avoiding trauma-related people, places, or activities).

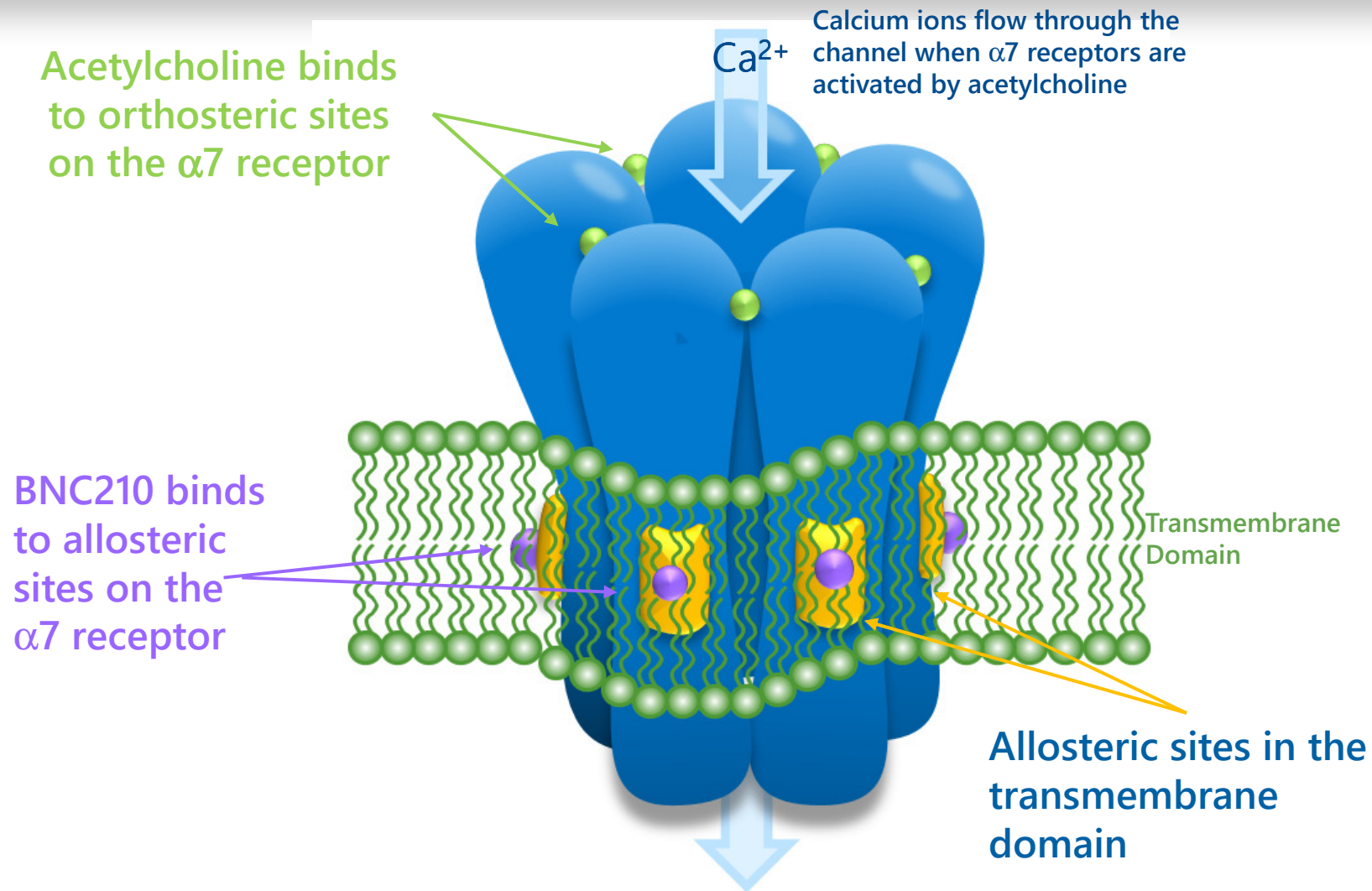
D. Negative alterations in cognition and mood that are associated with the traumatic event (2/7) (e.g., dissociative amnesia, negative perception of self and world, anhedonia, social withdrawal).

E. Alterations in arousal and reactivity (2/6) (e.g., irritability, aggression, problems concentrating, sleep disturbances, and hypervigilance).

What is BNC210?

- ❖ BNC210 is a truly novel anxiolytic compound, with antidepressant properties, developed by Bionomics;
- ❖ BNC210 selectively targets the alpha 7 nicotinic acetylcholine receptor ($\alpha 7$ nAChR);
- ❖ BNC210 is a negative allosteric modulator (NAM) of the $\alpha 7$ nAChR (electrophysiology; binding studies)
- ❖ The lack of side effects of BNC210 is unique and appealing to both patients and practitioners.

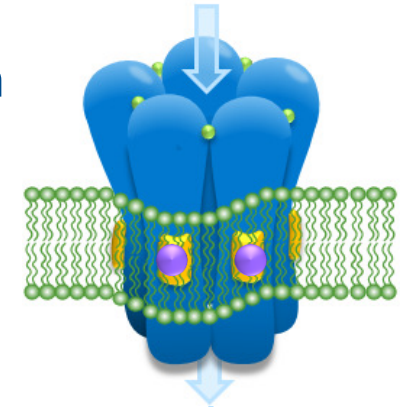
$\alpha 7$ Nicotinic Acetylcholine Receptor: A perfect target for allosteric modulation



Five alpha subunits make up the $\alpha 7$ receptor=Five potential binding sites

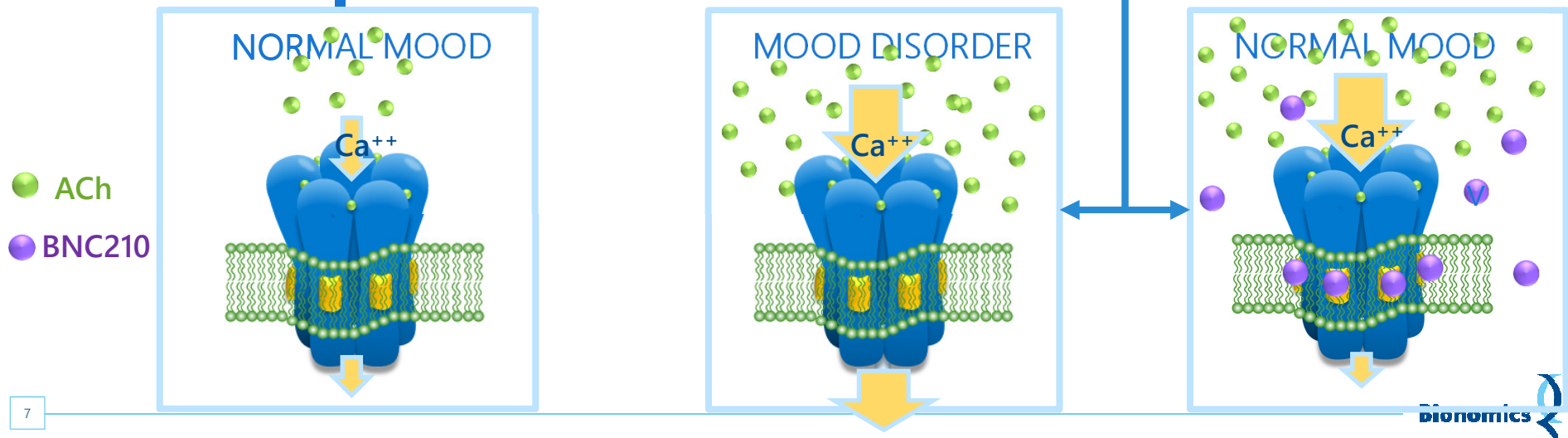
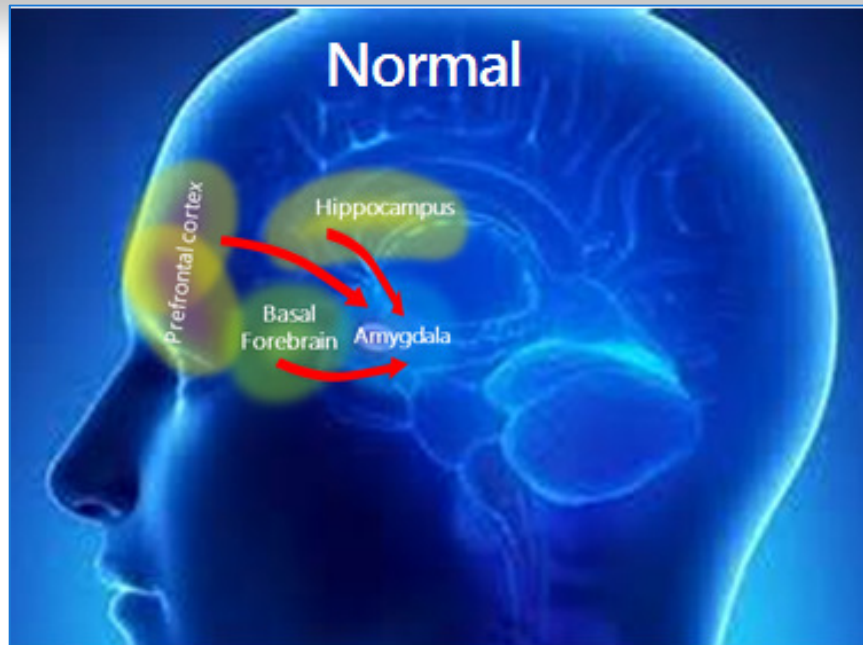
Negative allosteric modulators (NAMs) have many advantages over antagonists and channel blockers

- ❖ Don't bind to orthosteric site or compete with acetylcholine
- ❖ Highly selective molecules
- ❖ SAFE: no effect on receptor alone, only influence is when ligand is bound,
- ❖ Preserve signaling and kinetics of receptor - just tune up or down
- ❖ A natural ceiling to magnitude of effect
- ❖ Efficacy over a broad dose range, no u-shaped dose response



NORMALISE RECEPTOR ACTIVITY

BNC210 Action Depends on Acetylcholine Neurotransmission



BNC210 has undergone extensive efficacy and safety profiling prior to entry into the clinic

- ✓ Light Dark Box
- ✓ Marble Burying
- ✓ Contextual Fear Conditioning
- ✓ Elevated Plus Maze

MICE

- ✓ Elevated Plus Maze
- ✓ Pre-stress + Elevated Plus Maze
- ✓ CCK + Elevated Plus Maze
- ✓ Forced Swim Test

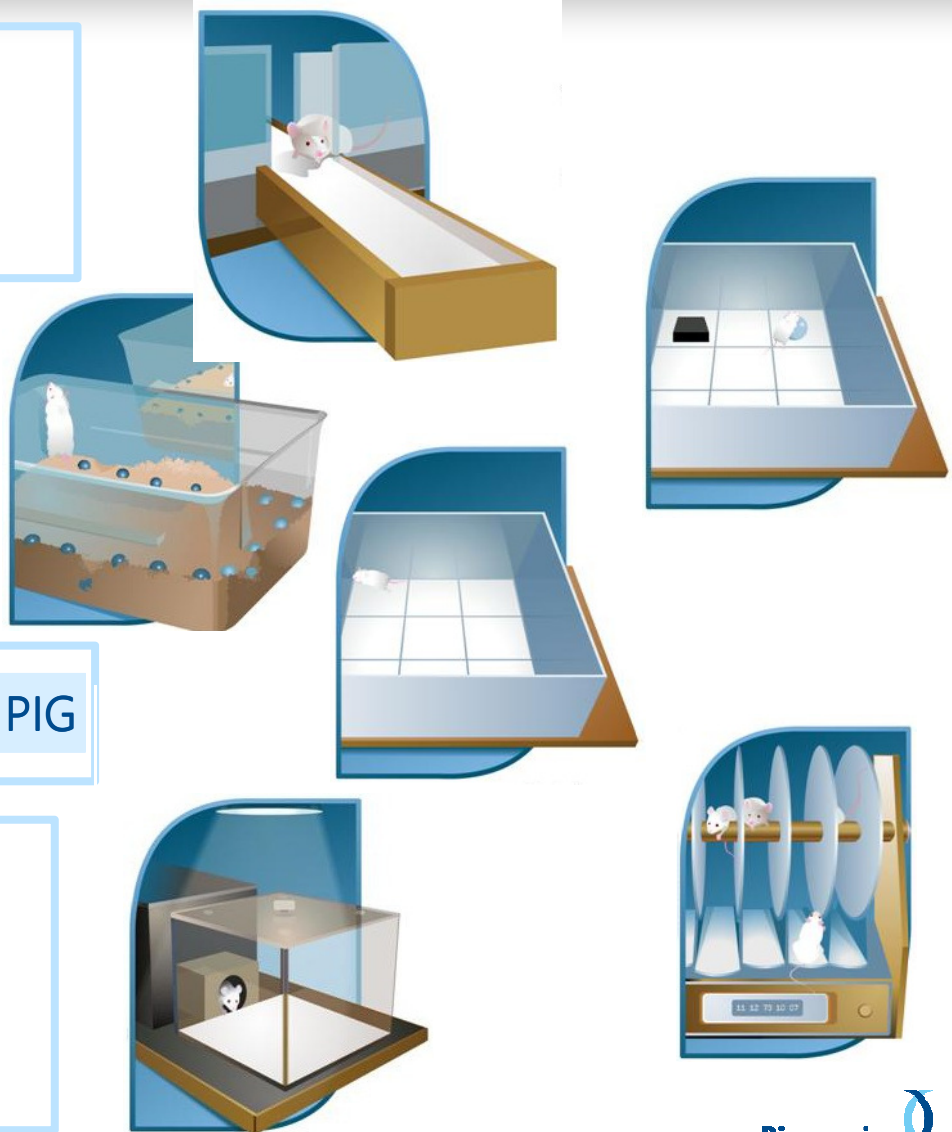
RAT

- ✓ Isolation-induced vocalizations in guinea pig pups

GUINEA PIG

- Open Field – dark, light
- Rotarod
- Modified Irwin
- Novel Object Recognition
- T-maze

SAFETY



BNC20 clinical data has demonstrated anxiolytic activity while maintaining a unique safety profile

Protocol Number	Phase	Description	Subjects	Location
SAFETY AND TOLERABILITY		Safety and Tolerability of Single Ascending Doses	24	Australia
SAFETY AND TOLERABILITY LORAZEPAM COMPARISON		Lorazepam & BNC210 Comparison plus EEG	22	France
EFFICACY	1b	Panic Attack Model in Healthy Volunteers	59	France
SAFETY AND TOLERABILITY TARGET ENGAGEMENT		Safety and Tolerability of Multiple Ascending Doses Target Engagement Study with Nicotine and EEG	42	France
EFFICACY	2a	Imaging and Behavioural Study In Generalised Anxiety Disorder Patients	24	UK
EFFICACY	2	Post Traumatic Stress Disorder	Recruiting	Australia USA

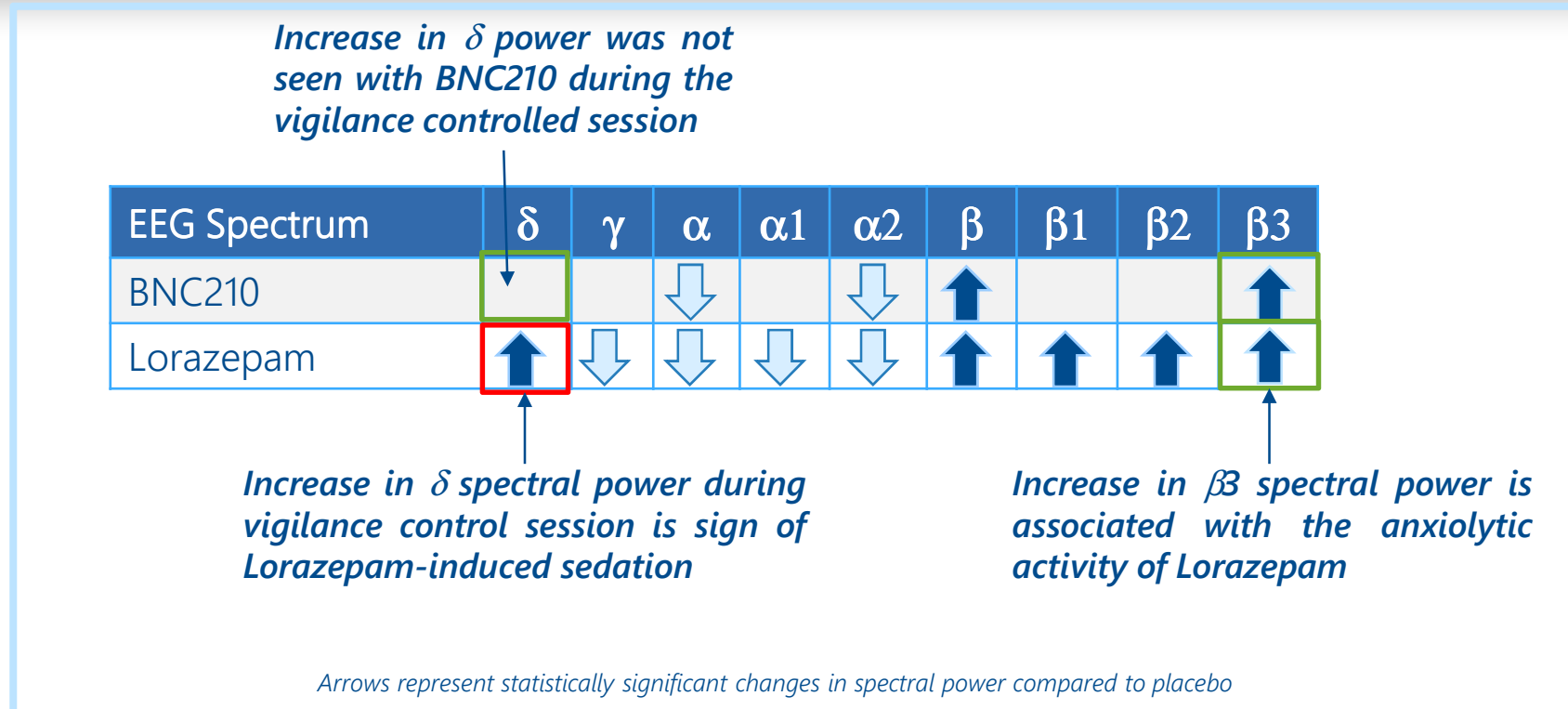
Single and multiple doses of BNC210 show no impairment of cognition or mood, no sedation and no abuse potential in humans

Assessments	*SINGLE DOSES Lorazepam Comparison Study		^ REPEAT DOSING 8-DAYS Multiple Ascending Dose Study
	BNC210 300, 2000 MG	LORAZEPAM	BNC210 ALL DOSES
Attention Multiple Choice Reaction Time	No effect	Slowed	No effect
Psychomotor Speed /Sustained Attention /Working memory Digital Substitution Test	No effect	Slowed	No effect
Visual/motor Co-ordination; Sleep Saccades	No effect	Slowed	N/D
Emotion eVAS	No effect	Lower scores	No effect
Sleep Karolinska Sleepiness Scale	No effect	Sedative	N/D
Verbal Memory Perceptual Priming Test	No effect	Impaired	No effect
Numeric Working Memory	N/D	N/D	No effect
Spatial working memory	N/D	N/D	No effect
Addiction Potential ARCI49	No effect	Association with LSD and Phenobarbital/ Alcohol Group	No effect

* **Lorazepam Comparison Study** Single doses of BNC210 (300 and 2000 mg), Lorazepam (2 mg) and placebo. N=24 healthy volunteers.

^ **Multiple Ascending Dose Study** Assessed Day 1 and Day 8. N=6 for 300, 600 and 1200 mg/day; N=24 for 2000 mg/day, N=2 and 6 for placebo. All healthy volunteers.

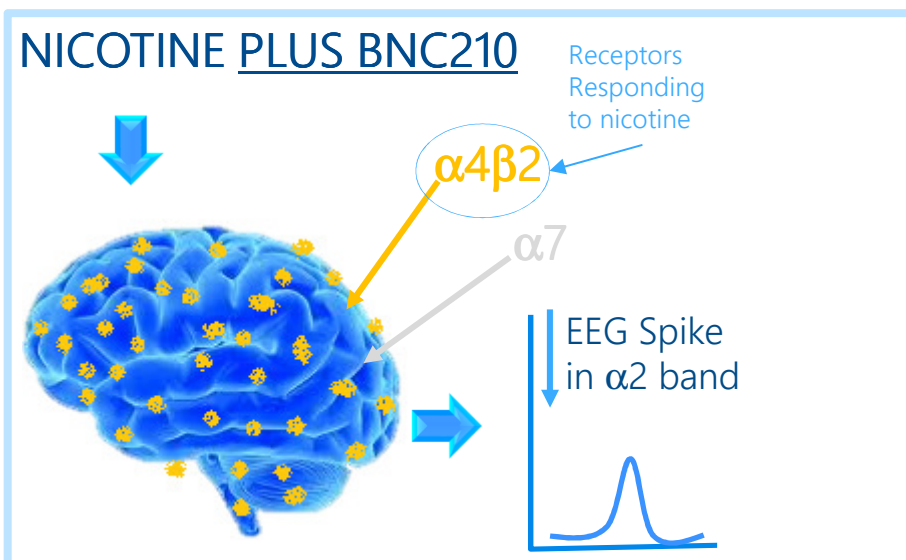
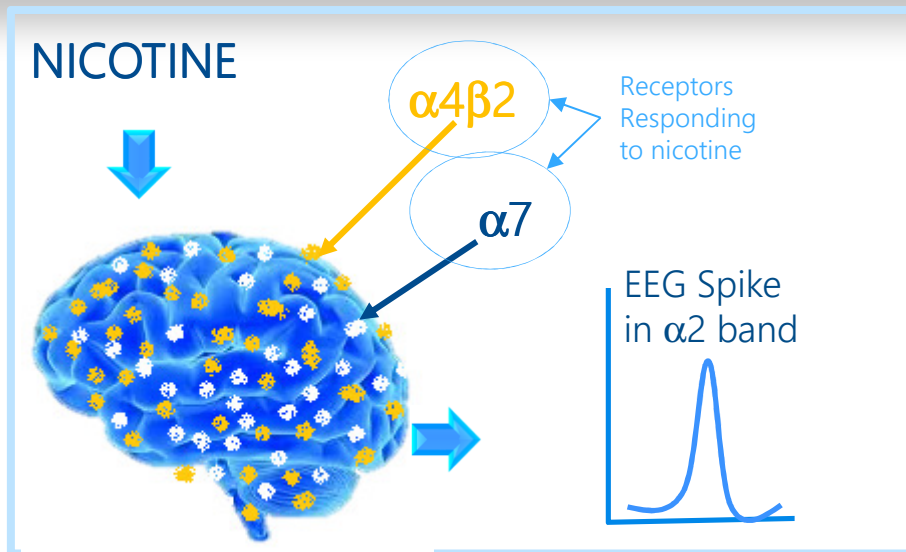
qEEG study confirmed BNC210 brain penetration, lack of sedation and a unique EEG signature compared Lorazepam



qEEG showed:

- BNC210 effects detected in the brain
- BNC210 is not sedating
- BNC210 and Lorazepam share an EEG response associated with the anxiolytic effects of Lorazepam

The nicotine-shift assay: nicotine-induced EEG responses provide evidence of BNC210 target engagement

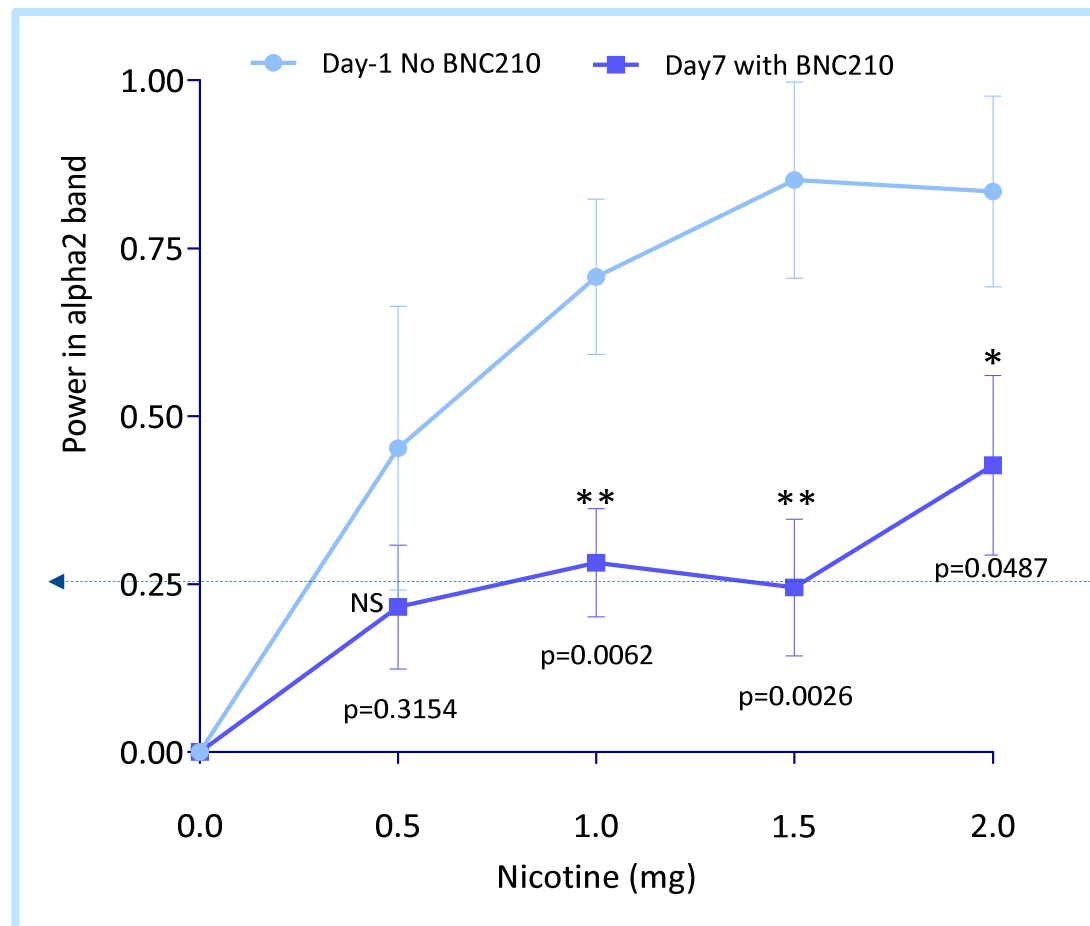


- Subjects treated with BNC210 will have reduced responses to nicotine if BNC210 binds to and inhibits the $\alpha 7$ receptor.
- BNC210 does not have an effect on $\alpha 4\beta 2$ so the block of the EEG response will be partial, not full.
- The contribution to the spike amplitude may be greater from $\alpha 4\beta 2$ receptors because nicotine is a more potent and efficacious agonist at $\alpha 4\beta 2$ (EC₅₀ 0.35-5 μ M) compared to $\alpha 7$ (49-113 μ M).

BNC210 modulates the activity of the $\alpha 7$ receptor in the human brain

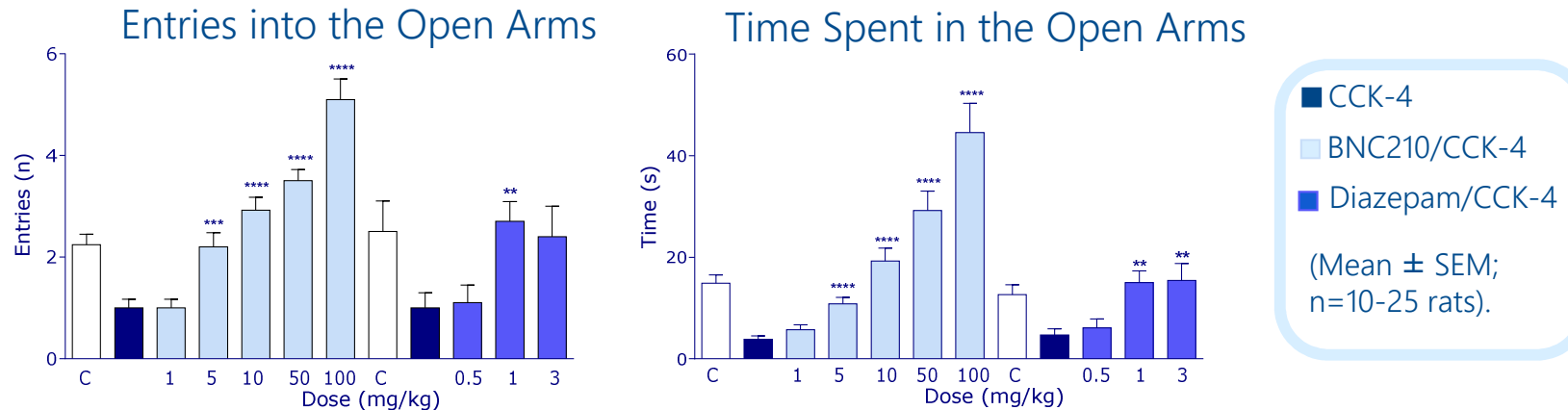
As the doses of nicotine increase from 0.5 to 2 mg, the amplitude of the spike in the $\alpha 2$ band increases. This is caused by nicotine activation of $\alpha 7$ and $\alpha 4\beta 2$ receptors.

- 2000 mg of BNC210 gives full block of the $\alpha 7$ receptor responses to 0.5, 1 and 1.5 mg of nicotine, leaving the residual response from $\alpha 4\beta 2$ receptors (~0.25 power)
- The $\alpha 4\beta 2$ response to 2mg of nicotine is not fully inhibited by 2000 mg BNC210

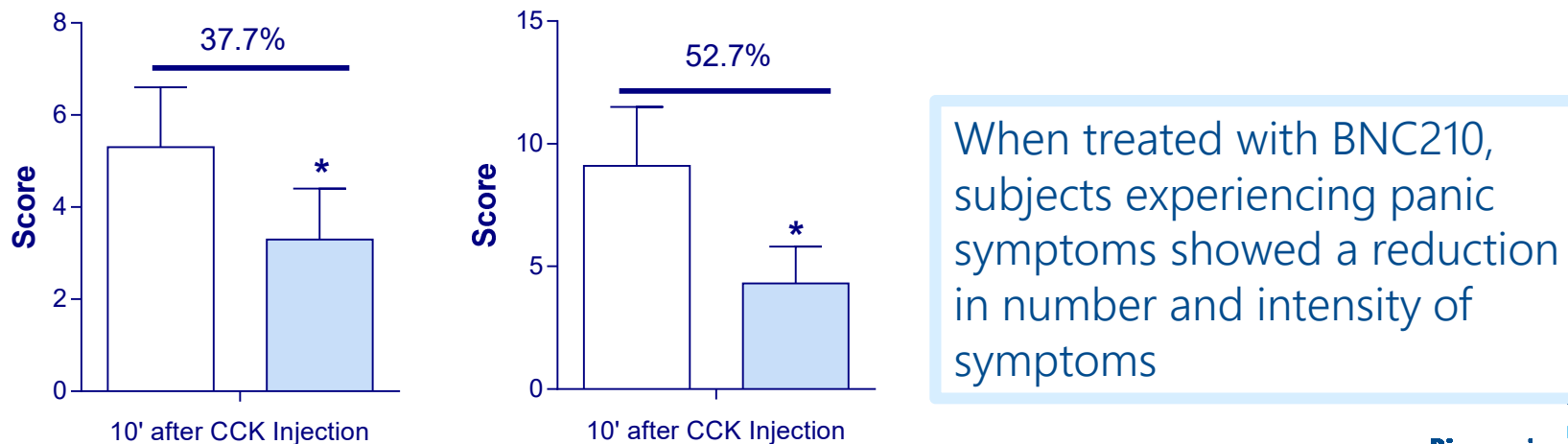


BNC210 significantly reduced CCK-4 induced panic symptoms in rodents and humans

RODENTS BNC210 Reversed the Anxiogenic Effect of CCK-4 in the Rat EPM

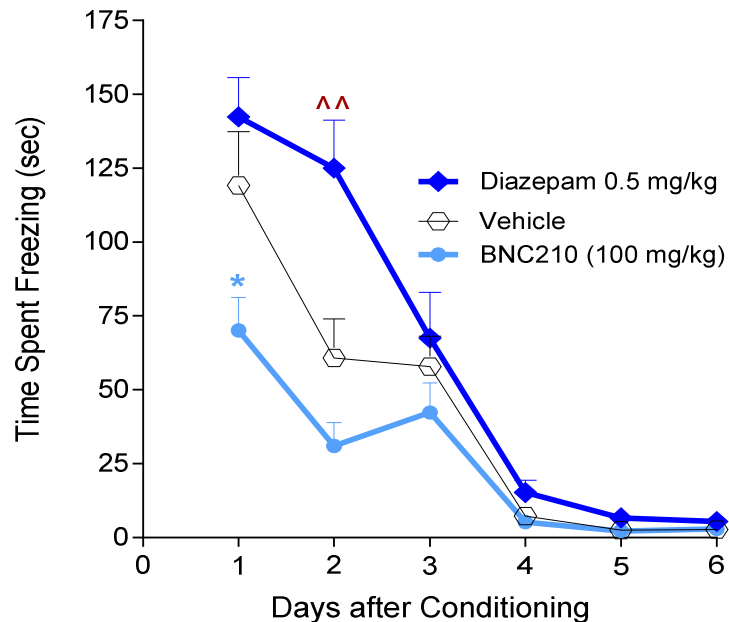


HUMANS % Reduction in Total Number of Symptoms and Symptom Intensity

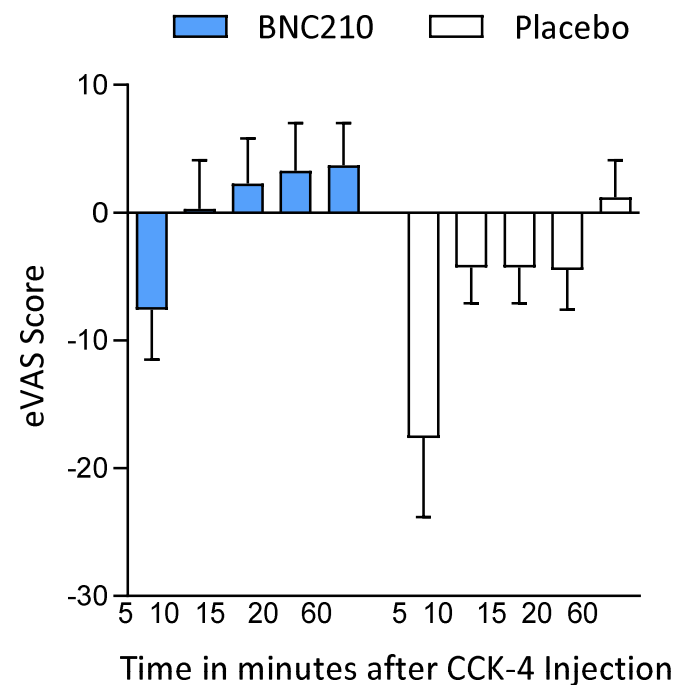


The effect of BNC210 on fear extinction in mice translated to improved emotional well-being following a CCK-4-induced panic attack in healthy volunteers

Conditioned Fear Extinction Model



Emotional Visual Analog Scale (eVAS)



MICE

BNC210 enhanced fear extinction following conditioned stimulus training

HUMANS

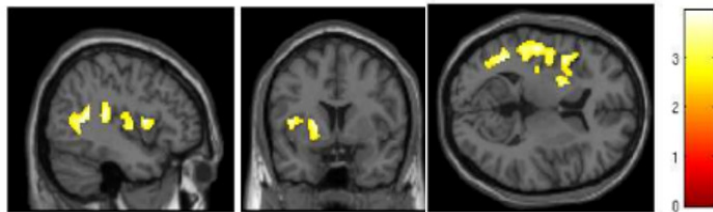
BNC210 improved rate of return to emotional stability following CCK-4 challenge

Phase 2 study in Generalised Anxiety Disorder patients - using fMRI to examine effects of BNC210 on neural correlates of anxiety

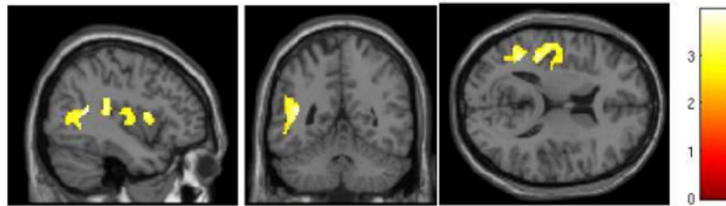
Title	A randomized, double-blinded, placebo & lorazepam-controlled, four-way crossover, Phase II study to evaluate the effects of single oral administration of BNC210 on brain activity changes captured by functional magnetic resonance imaging in adults with Generalized Anxiety Disorder
Protocol	BNC210.006
Study Centre	Institute of Psychiatry, Psychology and Neuroscience, King's College London
Design	Randomised, double-blind, placebo and Lorazepam-controlled, 4-way crossover (BNC210 300 and 2000 mg, Lorazepam 1.5 mg, Placebo)
Population	Un-medicated male or female volunteers with Generalized Anxiety Disorder
Subjects	24
Primary Objectives	(A) To determine whether BNC210 causes significant changes in cerebral perfusion using Arterial Spin Labelling (ASL) in the resting state. (B) To determine whether BNC210 causes significant changes in task-related brain activity using the emotional faces task during fMRI.
Secondary Objectives	To determine the effect on defensive behavior of two different oral doses of BNC210 using the Joystick Operated Runway Task and fMRI. To generate additional safety and tolerability information on BNC210.

Arterial spin labelling showed that BNC210 caused significant local changes in cerebral blood flow

BNC210 low dose >Placebo, all FWE corrected 0.05



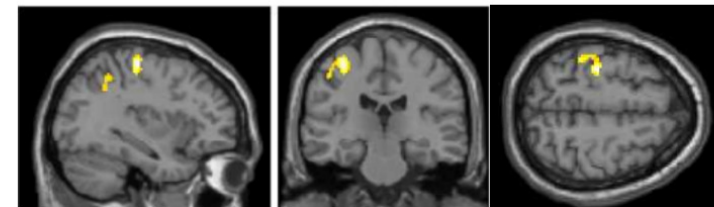
$P=0.047$, cluster size=356, peak located at -42/6/8



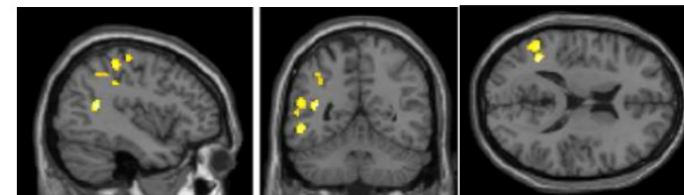
$P=1.72e-08$, cluster size=1758, peak located at -40/-50/14

Primary Endpoint

BNC210 high dose >Placebo, all FWE corrected 0.05



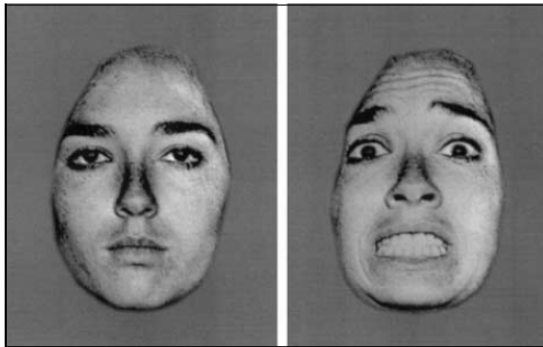
$P=0.030$, cluster size=387, peak located at -34/-24/58



$P=0.010$, cluster size=466, peak located at -40/-52/16

BNC210 caused significant changes in anxiety-related brain activity while viewing emotional faces during fMRI.

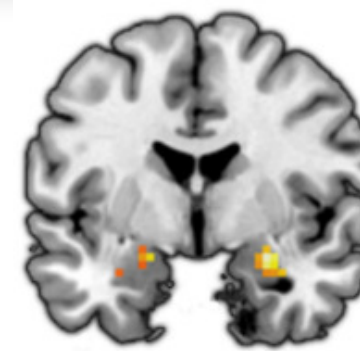
Emotional Faces Task



Thomas et al Arch Gen Psychiatry 2001 **58**, 1057-1063

← Neutral 20% 40% 60% 80% Fearful →

Primary Endpoint



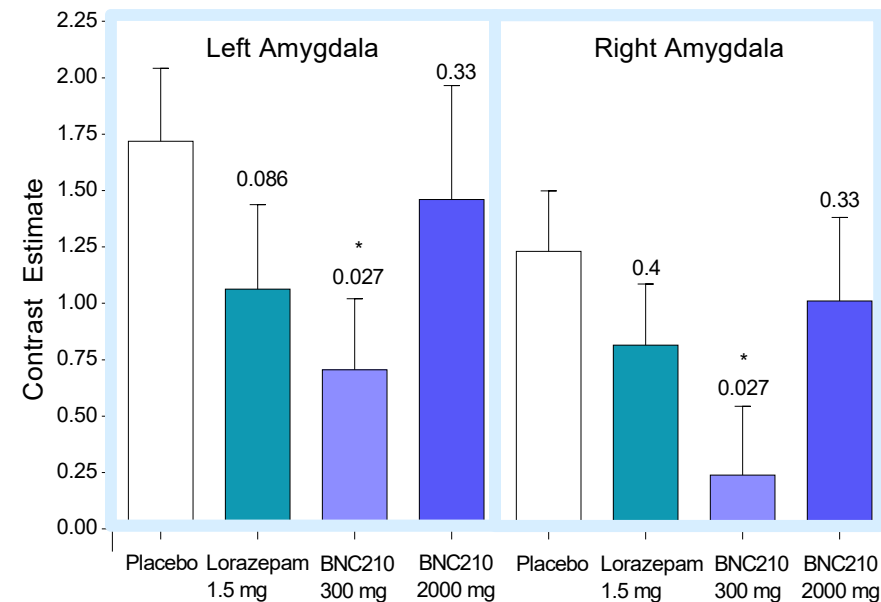
MALE?



FEMALE?

Decide whether this face is male or female and press left/right button

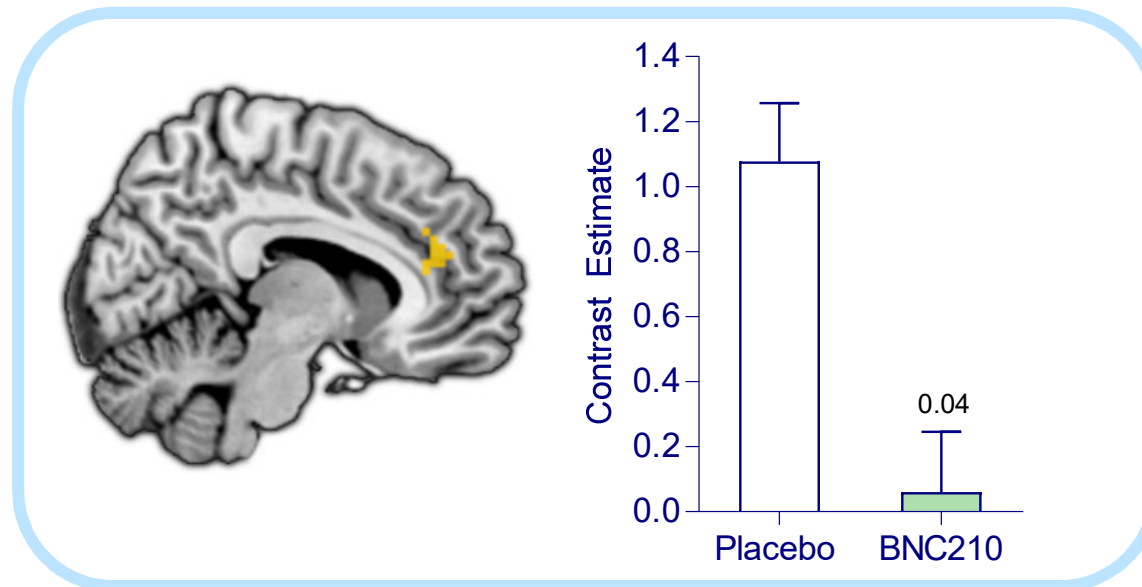
Fu et al Am. J. Psychiatry **164**, 599-607 (2007)



BNC210 Treatment Reduced Connectivity Between the Left Amygdala and the Anterior Cingulate Cortex in GAD Patients

BNC210 (300 mg) reduced connectivity between the left amygdala and anterior cingulate cortex (ACC) while viewing fearful faces

- increased positive coupling between these regions is associated with elevated threat processing under stress.
- In pathological anxiety this circuit becomes permanently 'switched-on'



This finding is highly supportive for the anxiolytic activity of BNC210

The Joystick Operated Runway Task (JORT) was used to model defensive behavior - threat avoidance

Measure of defensive behaviour

Flight intensity



Average velocity/
force used to escape
in trials with threat

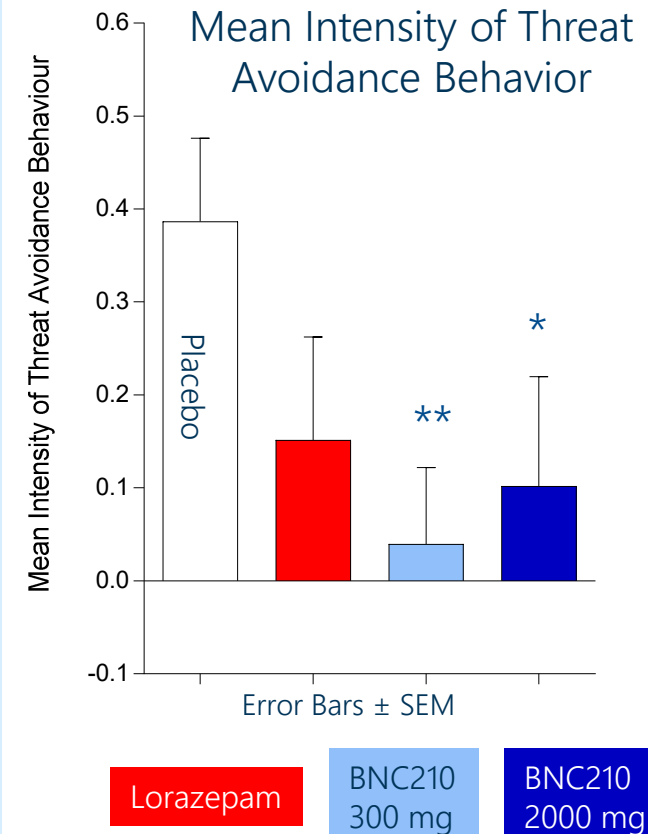


Average velocity/
force used to escape
in trials with no threat

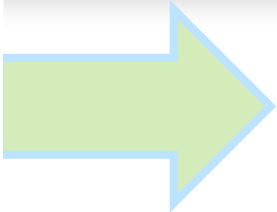
Joystick Operated Runway Task



Mean Intensity of Threat Avoidance Behavior



The potential advantages of BNC210, compared to standard anxiety treatments, have been demonstrated in preclinical and clinical studies



Standard of care treatment for anxiety is acute use of Benzodiazepines like Valium and Lorazepam and long term treatment with SSRIs or SNRIs like Prozac, Effexor, and Cymbalta

Potential Competitive Advantages of BNC210*

DRUG	Fast acting	No sedation	No memory impairment	No motor impairment	No withdrawal	No drug-drug interactions
BNC210	✓	✓	✓	✓	✓	✓
BZD	✓	X	X	X	X	✓
SSRI/SNRI	X	✓	✓	✓	X	X

**Based on data from preclinical studies and Phase 1 and 2 clinical trials*

A next generation anxiolytic like BNC210 will have broad therapeutic potential

Clinical data have provided sound evidence for the anxiolytic activity of BNC210

Anxiety Disorders

- Panic Disorder
- Generalized Anxiety
- Social Anxiety

- Animal and human behavioral data
- Effects on neural correlates of anxiety

Co-Morbid Anxiety

- Bipolar Disorder
- Major Depressive Disorder

Estimated Rates of Co-morbid Anxiety in:
Bipolar Disorder: 42-70%
Major Depression: ~50%
Dementia: ~20%
Schizophrenia (OCD): ~38%

Trauma and Stressor-Related Disorders

- PTSD

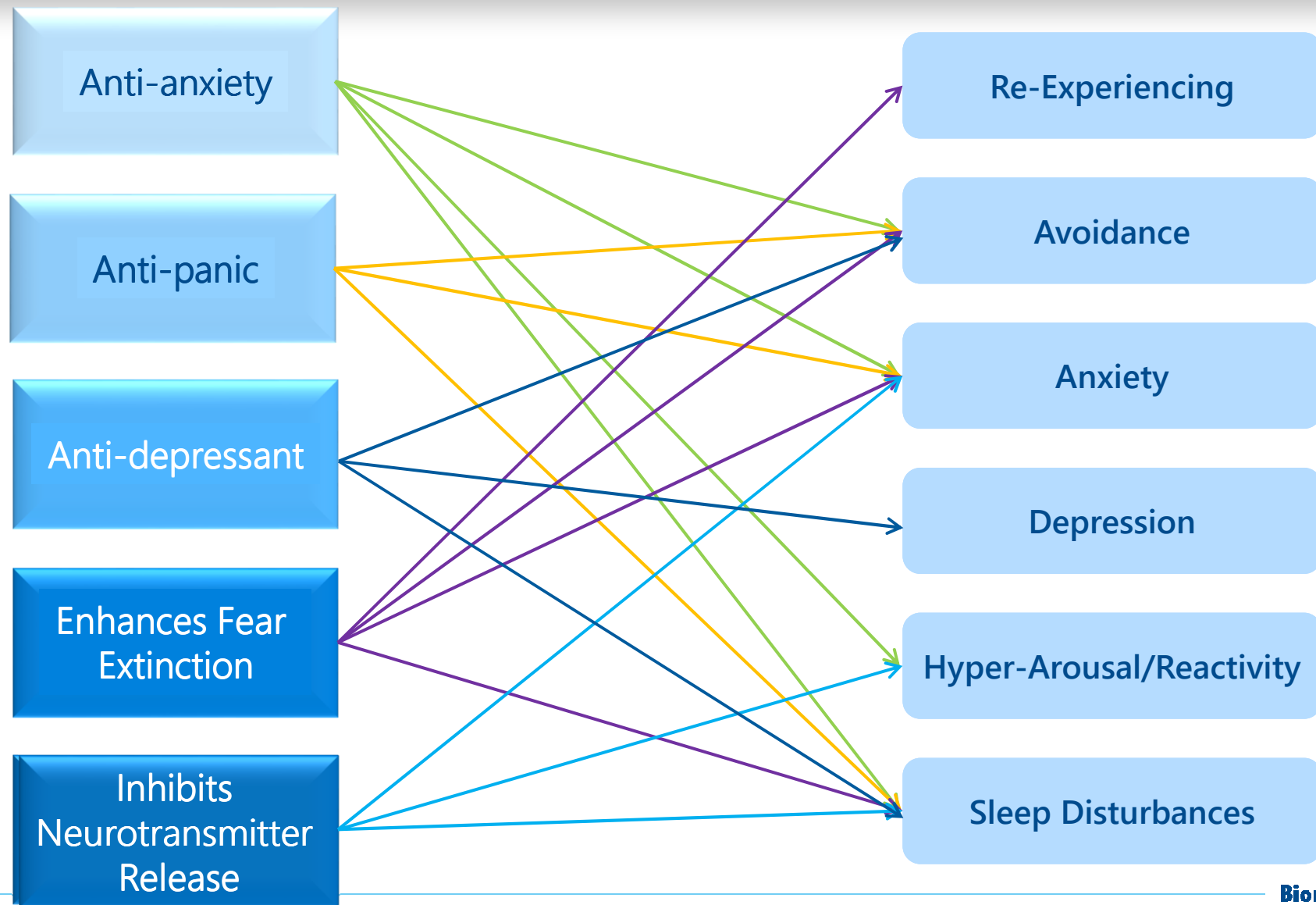
- Anxiolytic activity data generated in animals and humans
- Common underlying neural circuitry for anxiety and PTSD

Neurodegenerative Disease

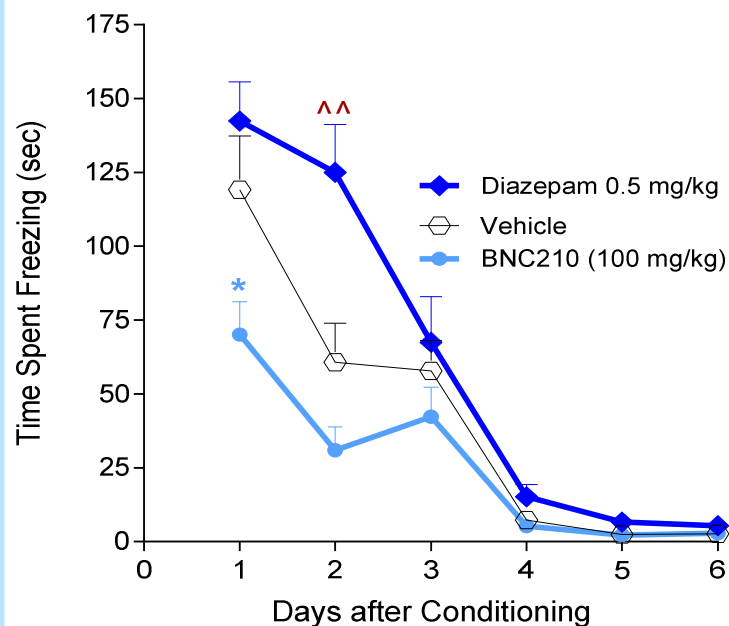
- Agitation and Anxiety

- Anxiolytic activity data generated in animals and humans
- Side effect and safety profile suitable for elderly

The Phase II trial in PTSD: The mechanism and pharmacology of BNC210 indicate its therapeutic potential for PTSD symptoms



Efficacy, safety and tolerability profiles of BNC210 provide an advantage over benzodiazepines for treatment of PTSD patients



	Day 1	Day 2
BNC210 vs Vehicle	*0.0318	0.06
BNC210 vs Diazepam	***0.0004	****0.0001
Vehicle vs Diazepam	NS	**0.01

Benzodiazepines have a negative effect on fear extinction in rodents and humans

VA/DoD recommend against the use of BZDs in the 'Practice Guideline for PTSD':

1. addiction liability
2. development of tolerance
3. cognitive impairment
4. motor impairment
5. sedation
6. lack of efficacy
7. overdosing
8. sudden unexplained deaths
9. car crashes
10. falls

VA has several initiatives in place to reduce prescriptions of BZDs to PTSD patients

50% increase in overall mortality rates associated with long-term use.

Bionomics is currently recruiting for a Phase 2 Trial in Post Traumatic Stress Disorder (PTSD) in Australia and the USA



SUBJECTS	192 PTSD patients
PROTOCOL	<ul style="list-style-type: none">• Double blind, placebo controlled, randomized, multi-centre• 4 arms: 1 placebo, 3 BNC210 dose levels• 12 weeks of dosing, twice daily oral treatment
PRIMARY OBJECTIVE	<ul style="list-style-type: none">• To determine whether BNC210 causes a decrease in PTSD symptoms as measured by CAPS-5
SECONDARY OBJECTIVES	<ul style="list-style-type: none">• To determine the effects of BNC210 on Anxiety (HAM-A), Depression (MADRS) and• Functioning and Quality of Life,• Safety and Tolerability
EXPLORATORY ENDPOINTS	Effects of smoking

RESTORE STUDY OVERVIEW

The RESTORE Study is a clinical research study evaluating a new experimental medication to see if it helps reduce the symptoms of PTSD and other associated symptoms including anxiety, depression, and sleep disturbances.



POST-TRAUMATIC STRESS DISORDER

**IT BEGINS WITH
A STORY**



<https://restorerresearchstudy.com/>

approach to managing PTSD. It is evaluating an experimental medication compared to placebo to see if it may help to reduce the symptoms of PTSD.

Don't let PTSD have the last word. Speak with us today.

Acknowledgements

BIONOMICS NEUROSCIENCE RESEARCH GROUP

**Carolyn Coles
Peter Kolesik
Deanna Mazzarolo
Yana Kolev
Ben Harvey
Chloe Hawkins
Danielle Mazurkiewicz
Litsa Karageorgos
Eden Dempsey**

**IN VIVO BIOLOGY
Emile Andriambeloson
Stephanie Wagner
Bertrand Huyard &
The Neurofit Team**

**CHEMISTRY
Walter & Eliza Hall Institute
Ian Street
*Brad Sleebs
Jonathan Baell**

**BIONOMICS
Dharam Paul &
BIONOMICS Chemistry Team**

PRESTWICK CHEMICAL

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