Peripheral Beta-Blockade Differentially Enhances Cardiac and Respiratory Interoception

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Abstract

Interoception, the perception of internal visceral states, arises from complex brain-body interactions across the central and peripheral nervous systems. Despite noradrenaline's key role in these interactions, its specific contribution to interoceptive processes remains unclear. In a placebo-controlled, randomised, within-subject study (N = 50), we employed computational modelling of interoceptive psychophysics to determine how pharmacological beta-adrenoceptor antagonism controls interoception across cardiac and respiratory domains. Both cardio-selective bisoprolol and non-selective propranolol improved cardiac perceptual sensitivity, with bisoprolol exerting an enhanced effect on cardiac metacognition. In contrast, both beta-blockers increased respiratory perceptual precision, with no corresponding changes in sensitivity or metacognition. These findings reveal a novel dissociation between central and peripheral beta-adrenergic mechanisms in interoception, highlighting the pivotal role of peripheral noradrenaline in regulating multi-organ brain-body interactions. Our results suggest that beta-blockers may provide promising routes for modulating distinct facets of interoception, potentially opening new avenues for intervention in conditions characterised by disrupted bodily self-awareness.

Keywords: Bayesian Modelling; Interoception; Psychophysics; Noradrenaline; Metacognition; Cardiac.

Introduction

Interoception is the ability to perceive and process signals related to the body's internal state, and its dysfunction is widely implicated in psychiatric conditions such as anxiety, depression, and panic disorders (Berntson & Khalsa, 2021; Paulus & Stein, 2010). Despite this clear importance, the neurobiological and neuropharmacological mechanisms underlying interoception remain poorly understood. Disentangling these mechanisms is a critical step toward understanding how interoceptive disturbances contribute to mental health conditions and how they may be targeted for intervention. Noradrenaline is a key neuromodulator in both the central and peripheral nervous systems, that is well-positioned to modulate interoceptive processing, and an ideal target for pharmacological manipulation (Aston-Jones & Cohen, 2005; Sara, 2009).

To determine whether peripheral and central beta-adrenergic pathways differentially influence interoception across cardiac and respiratory domains, we compared propranolol, a non-selective beta-blocker, with bisoprolol, a highly cardioselective beta-blocker. We utilised hierarchical Bayesian modelling of interoceptive psychophysics to assess whether these beta-blockers selectively modulate interoceptive sensitivity, precision, or metacognition across physiological domains.

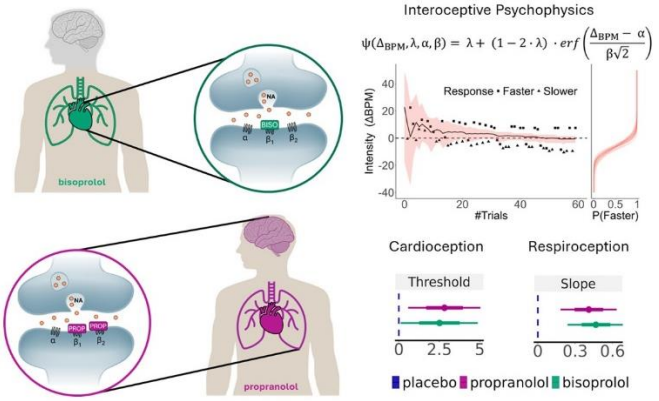

Figure 1: 50 participants completed two interoceptive psychophysical tasks under two pharmacologically distinct beta-blockers in this within-subject placebo-controlled study.

Methods

We conducted a randomised, double-blind, placebo-controlled, within-subject study in 50 healthy young adults. Participants received either propranolol, a non-selective beta-blocker that antagonises both β_1- and β_2-adrenoceptors and readily crosses the blood-brain barrier, or bisoprolol, a highly β_1-selective antagonist that does not cross the blood-brain barrier (Haeusler et al., 1986; Leopold et al., 1986). Given propranolol's broad noradrenergic inhibition and central effects, it allowed us to assess the contribution of both peripheral and central pathways, whereas bisoprolol's β_1-cardioselectivity enabled us to isolate the effects of targeted peripheral beta-adrenergic modulation. Consequently, we determined whether interoceptive processing is modulated by peripheral signalling alone or requires central noradrenergic involvement.

To independently assess cardiac and respiratory interoception, we employed two validated psychophysical tasks: the Heart Rate Discrimination Task (HRDT) and the Respiratory Resistance Sensitivity

Task (RRST) (Legrand et al., 2022; Nikolova et al., 2022). In the HRDT, participants classified an auditory tone as either "faster" or "slower" than their current heart rate. The RRST similarly required participants to compare two successive breaths and identify which contained a resistive load delivered via a computer-controlled inspiratory circuit. For both tasks, the stimuli (i.e., the tempo of auditory tones in the HRDT, and magnitude of resistive load in the RRST) were dynamically adjusted using a Bayesian adaptive algorithm (Kontsevich & Tyler, 1999).

We then applied hierarchical Bayesian modelling to estimate the following psychometric parameters: threshold (interoceptive sensitivity), slope (interoceptive precision), and lapse rate. The threshold represents the smallest detectable change in an interoceptive signal, with lower values indicating greater sensitivity to subtle internal fluctuations. A steeper slope indicates greater precision, as participants more reliably differentiate near-threshold stimuli with minimal uncertainty. Lapse rate captures the proportion of random or inattentive responses, allowing us to distinguish perceptual performance from errors due to lapses in attention or motor execution. To quantify metacognitive awareness (i.e., the alignment between trial-wise confidence and choice accuracy), we fitted a hierarchical ordered beta regression model to examine how propranolol and bisoprolol influence the alignment of interoceptive confidence with choice accuracy, while controlling for mean resting heart rate. These methodological advances enabled us to derive robust, interpretable estimates of interoceptive sensitivity, precision, and metacognition across physiological domains.

Results

In the HRDT, we observed a significant increase compared with placebo (pl) in interoceptive threshold under both propranolol (pr) (μ = 2.82, CI [0.57; 5.03], P(pl > pr) = .02) and bisoprolol (bi) (μ = 2.51, CI [0.11; 4.88], P(pl > bi) = .04), indicating improved sensitivity to heart rate under beta-blockade. In contrast, no significant effects were observed on the slope for propranolol (μ = -0.007, CI [-0.23; 0.20], P(pl > bi) = .50) or bisoprolol (μ = -0.03, CI [-0.17; 0.12], P(pl > bi) = .61), suggesting that beta-blockade did not alter cardioceptive precision. Similarly, no significant differences in lapse rate were found between propranolol (μ = 0.48, CI [-2.34; 2.94], P(pl > bi) = .34) or bisoprolol (μ = -1.19, CI [-3.88; 1.34], P(pl > bi) = .77) compared to placebo, indicating no change in the random/erroneous response rate under either drug condition. These results indicate that beta-blockade selectively enhances cardiac interoceptive sensitivity, without affecting lapse rate. Both drugs also increased metacognitive awareness in the HRDT, with propranolol (pr × accuracy: β = 0.88, CI [0.79; 1.00], p = .045) and bisoprolol (bi × accuracy: β = 0.85, CI [0.75; 0.96], p = .008) influencing confidence for correct versus incorrect responses.

In the RRST, slope estimates were significantly higher under both propranolol (μ = 0.41, CI [0.18; 0.63], P(pl > pr) = .002) and bisoprolol (μ = 0.47, CI [0.24; 0.69], P(pl > bi) = .0004) compared to placebo, indicating improved respiroceptive precision. No significant differences were found for threshold (μ = 0.16, CI [-0.20; 0.52], P(pl > pr) = .23; = -0.08, CI [-0.44; 0.27], P(pl > bi) = .65) or lapse rate (pr: μ = -1.23, CI [-2.49; 0.39], P(pl > pr) = .90; bi: μ = -0.80, CI [-2.20; 0.72], P(pl > bi) = .83), suggesting that beta-blockade did not affect respiroceptive sensitivity or random response tendencies. Overall, these results indicate that beta-blockade selectively enhances the precision of respiratory signal processing, while leaving detection thresholds and response consistency intact.

In summary, we demonstrate that central and peripheral noradrenergic beta-blockade exerts distinct effects on interoceptive sensitivity, precision, and metacognition across cardiac and respiratory domains. Both beta-blockers enhanced cardiac interoception, with bisoprolol showing a stronger effect on metacognitive awareness, while respiratory interoception was modulated through increased precision without changes in sensitivity or metacognition. We reveal a domain-specific dissociation in the mechanisms by which noradrenaline influences interoception and highlights distinct autonomic pathways as potential targets of future therapeutic interventions for psychiatric disorders.

For related works see: (Tyrer et al., 2025)

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