BI-03 From hormones to emotion and action

The study of behavioral neuroendocrinology—the investigation of how hormones and neuropeptides shape, and are shaped by, human emotion and action—has undergone a profound paradigm shift. For decades, the literature was characterized by biological determinism and an eagerness to assign singular behavioral functions to specific molecules. Testosterone was labeled the "aggression hormone," oxytocin was dubbed the "cuddle chemical," and the fluctuations of estradiol and progesterone were viewed predominantly through the lens of deficit and pathology. However, as sample sizes have expanded, as preregistration has become the norm, and as meta-analytic techniques have matured, a highly nuanced, context-dependent, and conditionally constrained picture has emerged.

To rigorously understand the causal evidence linking sex hormones and neuropeptides to human behavior, it is necessary to cleanly separate the phenomenon into three distinct but interacting layers. The first is the **physiology** layer. This is the realm of the measurable and the mechanistic: circulating serum titers, pharmacokinetic half-lives, receptor density, allosteric modulation, and the penetration of the blood-brain barrier. The second is the **behavioral** layer. Behavioral outputs are inherently statistical; they exist as overlapping probability distributions between populations (e.g., men and women) rather than binary sexually dimorphic traits. What is true of a population average tells us remarkably little about the behavioral trajectory of a specific individual. The third layer is **culture**. Hormones do not operate in a vacuum; they provide a motivational valence that culture channels. If a biological mechanism promotes status-seeking, it is culture that dictates whether that status is achieved through physical aggression, the accumulation of wealth, or conspicuous acts of altruism.

This report systematically reviews the causal evidence linking testosterone, estradiol, progesterone, oxytocin, vasopressin, and cortisol to emotional experience and behavior. It prioritizes double-blind, placebo-controlled administration studies, robust meta-analyses, and large-scale registered replications to present a definitive foundation for understanding how human biology interacts with social environments.

Testosterone: The Myth and Reality of the Status Hormone

For over a century, testosterone has been inextricably linked in the scientific and public imagination with aggression, hostility, and antisocial behavior. Originating with Berthold's 19th-century castration experiments on roosters, the assumption that endogenous and exogenous androgens strictly drive physical violence in humans has been a persistent theoretical anchor[1]. However, recent rigorous meta-analyses and large-scale pharmacological challenge studies reveal a much more complex reality, dismantling the simple androgenic-drive narrative.

The Weak Link to Aggression

The most comprehensive quantitative synthesis of the testosterone-aggression link in humans

was conducted by Geniole, Bird, McVittie, Purcell, Archer, and Carré, published in *Hormones and Behavior* in 2020[2]. Analyzing decades of literature spanning baseline associations, dynamic changes, and pharmacological manipulations, the meta-analysis revealed that the relationship between testosterone and aggression is remarkably weak and highly conditional.

Baseline circulating testosterone shared a very weak, albeit statistically significant, positive association with aggression across humans (r = 0.054, 95% CI [0.028, 0.080])[2]. When disaggregated by sex, the effect was significant in men (r = 0.071, 95% CI [0.041, 0.101]) but indistinguishable from zero in women (r = 0.002, 95% CI [-0.041, 0.044])[2]. Dynamic changes in testosterone—spikes in the hormone in response to competition or environmental provocation—were slightly more predictive of aggressive behavior (r = 0.108), again showing a stronger effect in men (r = 0.162) than in women (r = 0.010)[4].

Crucially, the causal evidence derived from double-blind, placebo-controlled administration of exogenous testosterone failed to show a statistically significant main effect on aggression (r = 0.046, 95% CI [-0.015, 0.108])[2]. The failure of exogenous administration to reliably and universally induce aggression refutes the simplistic physiological model that testosterone inevitably triggers violence[5]. Instead, researchers propose that testosterone's effects are highly moderated by individual personality traits (such as trait dominance and impulsivity) and environmental provocation[2]. At the behavioral layer, this means that administering testosterone only increases aggressive responses in individuals already predisposed to high trait dominance or when they are actively socially excluded or threatened[3].

Meta-Analytic Approach (Geniole et al., 2020)	**Overall Effect Size (r)**	**95% Confidence Interval**	**Statistical Significance**
Baseline T & Aggression	0.054	[0.028, 0.080]	Significant (Weak)
Baseline T & Aggression (Men)	0.071	[0.041, 0.101]	Significant (Weak)
Baseline T & Aggression (Women)	0.002	[-0.041, 0.044]	Not Significant
Dynamic T Change & Aggression	0.108	[0.041, 0.174]	Significant (Weak)
Manipulated T	0.046	[-0.015, 0.108]	Not Significant

(Causal Effect)			

Status-Seeking and Economic Preferences

If testosterone does not reliably cause aggression, what is its primary behavioral function? Modern consensus relies on the "Challenge Hypothesis" and broader life-history frameworks, which posit that testosterone primarily regulates motivation for *status-seeking* and the protection of social rank during times of challenge[10].

Because human social hierarchies are complex, status is rarely achieved through unprovoked violence. In many cultural contexts, status is achieved through fairness, reputation-building, and calculated generosity. This cultural layer explains a series of seemingly contradictory findings in behavioral economics. Early work by Zak et al. (2009) found that testosterone administration decreased generosity in the Ultimatum Game, leading to the assumption that the hormone promotes selfish behavior[12]. However, Eisenegger et al. (2010) demonstrated that women given sublingual testosterone actually made *fairer* bargaining offers in the Ultimatum Game, provided they believed they were protecting their status from the risk of social rejection[7]. Furthermore, Dreher et al. (2016) found that testosterone increased the punishment of unfairness but also increased rewards for large, generous offers in men, suggesting the hormone amplifies whatever behavior best signals dominance and social value in the immediate context[7].

Yet, even the status-seeking hypothesis has faced intense recent scrutiny due to the replication crisis. Small sample sizes in early economic game studies led to a high risk of false positives. In a massive, preregistered, double-blind randomized controlled trial involving 1,000 male participants, Nadler, Zava, Camerer, and colleagues (2024) found absolutely no evidence that a single 11 mg dose of intranasal testosterone affected economic preferences, trust, competitiveness, or risk-taking[13]. This null finding in a highly powered sample challenges the view that short-term exogenous testosterone fluctuations meaningfully and predictably shape human economic preferences in a laboratory vacuum, emphasizing that cultural context and real-world stakes may be necessary to activate status-seeking biological pathways[13].

The Dual-Hormone Hypothesis

To account for inconsistencies in the testosterone literature, the Dual-Hormone Hypothesis was proposed, suggesting that testosterone's positive association with status-seeking and aggression is conditionally dependent on the hypothalamic-pituitary-adrenal (HPA) axis—specifically, it requires *low* levels of cortisol[10]. When cortisol (a biomarker of stress and social avoidance) is high, the behavioral effects of testosterone are theorized to be blocked or suppressed[10].

While theoretically elegant at the physiological layer, the Dual-Hormone Hypothesis has struggled under strict meta-analytic evaluation. A comprehensive meta-analysis by Dekkers et al. (2019) (N = 8,538, 33 studies, 49 effect sizes) found only marginal support for the hypothesis[16]. The interaction effect between testosterone and cortisol on status-relevant behavior was statistically significant but practically negligible in magnitude (r = -0.061, p =

0.026)[16]. Consequently, while cortisol undoubtedly interacts with the hypothalamic-pituitary-gonadal (HPG) axis physiologically, the statistical reliability of the dual-hormone interaction as a macroscopic predictor of human behavior remains heavily contested. What is statistically significant in a population average (r = -0.061) offers almost zero predictive validity for how a specific individual will behave under stress.

Cognitive Empathy: The RMET Controversy

Another prominent theory posited that testosterone reduces cognitive empathy—the ability to accurately read the emotions and intentions of others. This theory was famously supported by a study which found that administering testosterone to 16 young women significantly impaired their performance on the Reading the Mind in the Eyes Test (RMET)[18]. The researchers also claimed this impairment was moderated by the 2D:4D digit ratio, a putative marker of prenatal testosterone exposure, seemingly validating the "Extreme Male Brain" theory of empathy deficits[18].

However, this finding failed to replicate when subjected to rigorous, highly powered conditions. A preregistered replication involving 243 healthy men receiving either a placebo or transdermal testosterone gel found no main effect of testosterone on RMET performance, nor any moderation by the 2D:4D ratio[18]. The initial finding is now widely viewed by critics as an artifact of a severely underpowered sample (N = 16) and subsequent publication bias[18]. Furthermore, pharmacokinetic differences play a role: early studies relied on sublingual administration in women, which creates supraphysiological spikes in serum levels, whereas modern studies utilize FDA-approved gels (e.g., 100-150 mg transdermal or 11 mg intranasal) that mimic high-normal physiological ranges, ensuring that behavioral observations reflect plausible biological realities[8].

Estradiol, Progesterone, and the Architecture of Mood

The female reproductive cycle involves dynamic, systemic fluctuations in estradiol and progesterone. While the majority of women navigate these fluctuations without severe psychiatric impairment, a subset experiences profound affective disruptions, providing a critical window into the causal role of female sex steroids in the central nervous system.

PMDD and Receptor Sensitivity

Premenstrual Dysphoric Disorder (PMDD) affects roughly 5% of women and is characterized by severe depressed mood, anxiety, irritability, and affective lability during the luteal phase of the menstrual cycle[21]. Historically, PMDD was assumed to be driven by a physiological "hormone imbalance"—an absolute deficit or excess of circulating estradiol or progesterone.

Rigorous causal experiments have definitively disproven the imbalance theory. Landmark work by Schmidt, Rubinow, and colleagues (1998; 2017) utilized a gonadotropin-releasing hormone (GnRH) agonist (leuprolide) to suppress ovarian function in 22 women with PMDD (ages 30 to 50), which effectively eliminated their affective symptoms within two to three months[22]. When the researchers subsequently administered a continuous, steady-state, single-blind add-back of combined estradiol and progesterone, the women experienced a severe reinstatement of PMDD symptoms during the first month[22]. Strikingly, however, during the second and third

months of continuous steady-state hormone administration, the symptoms vanished[21].
This provides a profound second-order insight into neuroendocrinology: the brain is a difference engine. Women with PMDD do not have abnormal absolute levels of hormones; rather, they suffer from an abnormal, heightened central nervous system sensitivity to the *rate of change* (the physiological delta) of ovarian steroids from low to high[21].

The Role of Allopregnanolone

Mechanistically, the affective distress linked to the luteal phase is heavily mediated by allopregnanolone, a neuroactive steroid metabolite of progesterone. Allopregnanolone is a potent positive allosteric modulator of the GABA-A receptor, the primary inhibitory neurotransmitter system in the brain[24]. During the luteal phase, allopregnanolone levels rise and then abruptly fall. In healthy women, GABA-A receptors adapt to these fluctuations seamlessly. In women with PMDD, there is an impaired plasticity of the GABA-A receptor response to dynamic allopregnanolone fluctuations, leading to heightened excitability, anxiety, and irritability[24].
This mechanistic understanding has revolutionized treatment. For instance, low doses of the selective serotonin reuptake inhibitor (SSRI) fluoxetine are highly effective for PMDD and operate much faster than they do for major depressive disorder. Researchers have demonstrated that low-dose fluoxetine acts not merely by blocking serotonin reuptake, but by functioning as a selective brain steroidogenic stimulant[26]. It rapidly increases the synthesis of allopregnanolone in the brain and prevents its oxidation into 5α-dihydroprogesterone, thereby stabilizing GABAergic inhibition independently of traditional serotonergic pathways[25].

Cognition, Memory, and Spatial Ability

Beyond affect, estradiol modulates cognitive architecture, particularly working memory and spatial processing. Meta-analyses highlight that mental rotation and spatial abilities tend to fluctuate slightly across the menstrual cycle, often peaking during menses (when estradiol is low) and dipping during the mid-luteal phase (when estradiol and progesterone are high)[29]. Conversely, verbal memory and fluency frequently benefit from estrogenic peaks, though declines are noted in older populations experiencing natural estrogen withdrawal[32].
Neuroimaging provides insight into the physiological layer of these behavioral observations. fMRI studies comparing women on and off estradiol treatment during an N-back working memory task show that while behavioral accuracy does not significantly differ (often due to ceiling effects in healthy subjects), women treated with estradiol show significantly increased frontal cortex activation during high-load cognitive conditions (2-back and 3-back)[34]. Estradiol, therefore, acts as a permissive neuromodulator that alters the metabolic and neural strategies the brain uses to maintain performance under cognitive load, even if the absolute behavioral output remains statistically equivalent[34].

Oxytocin and Vasopressin: The Replication Crisis of the "Cuddle Chemicals"

No neuropeptides have been more aggressively popularized—and subsequently heavily corrected by rigorous replication—than oxytocin and arginine vasopressin. Initially celebrated

as evolutionary panaceas for trust, bonding, and empathy, the current empirical landscape is defined by conditional effects, extreme in-group bias, and severe methodological skepticism regarding administration routes.

Trust and the Replication Crisis

In 2005, a landmark paper published in *Nature* (Kosfeld et al.) claimed that intranasal oxytocin increased trusting behavior in a neuroeconomic Trust Game, analyzing a small sample of 58 participants[36]. This sparked a decade of research equating oxytocin with prosociality. However, subsequent highly powered replication attempts systematically failed to verify the main effect of oxytocin on trust. A meta-analysis and systematic review by Nave, Camerer, and McCullough (2015) evaluated the literature and found that six independent studies completely failed to replicate the original Kosfeld findings[37]. Building on this skepticism, Declerck et al. (2020) conducted a massive, preregistered, double-blind, placebo-controlled replication (N > 300), explicitly testing the oxytocin-trust link under various social contact conditions[37]. They found zero main effect of oxytocin on trusting behavior, confirming that the early, sensationalized findings were highly likely to be false positives driven by small sample sizes and publication bias[40].

Study / Meta-Analysis	Focus Area	Sample Size	Key Finding	Replication Status
Kosfeld et al. (2005)	Oxytocin & Trust Game	N = 58	OT increases financial trust	Original Claim
Nave et al. (2015)	Oxytocin & Trust	6 Studies	Failed to find robust OT-trust link	Meta-analytic Failure
Declerck et al. (2020)	Oxytocin & Trust	N > 300	No main effect of OT on trust	Preregistered Failure

Parochial Altruism: The Dark Side of Oxytocin

Where oxytocin *does* reliably modulate behavior, it does so through an evolutionary lens of group survival rather than universal benevolence. A series of landmark experiments by De Dreu et al. (2010; 2011) across 870 human participants (373 males, 497 females) demonstrated that oxytocin regulates "parochial altruism"[42].

In double-blind, placebo-controlled intergroup conflicts utilizing prisoner's dilemmas and ultimatum bargaining, oxytocin administration increased "in-group love" (cooperation, trust, and self-sacrifice for one's own group) but simultaneously heightened defensive "out-group hate" (prejudice, derogation, and defensive aggression against competing groups)[42]. In two specific Implicit Association Test (IAT) experiments (N = 63 against Arab out-groups; N = 70

against German out-groups), oxytocin significantly increased implicit in-group favoritism and out-group derogation compared to placebo[43].

At the physiological layer, oxytocin interacts with dopaminergic reward-processing circuits in the nucleus accumbens and amygdala-hippocampal circuitries to create intergroup bias. It shifts the biobehavioral approach-avoidance system to prioritize the safety and cohesion of familiar kin and ingroups at the explicit expense of outsiders[43]. This robustly dismantles the cultural narrative of oxytocin as a universal "cuddle chemical," reframing it as an evolutionary neurohormone designed to facilitate the fierce protection of the tribal unit in hostile environments.

The Intranasal Delivery Controversy

The behavioral oxytocin literature is currently facing an existential threat at the physiological layer. The vast majority of human behavioral studies rely on the intranasal administration of oxytocin (typically 24 IU to 40 IU), operating under the assumption that the peptide bypasses the blood-brain barrier via olfactory and trigeminal nerve pathways to directly bathe the central nervous system[47].

Leading critics, notably Leng and Ludwig (2016), have forcefully challenged this assumption[50]. Pharmacokinetic studies reveal that only microscopic fractions of intranasally applied oxytocin actually reach the cerebrospinal fluid[49]. Conversely, intranasal application causes massive, supraphysiological spikes in peripheral blood oxytocin, which binds to receptors in the gastrointestinal tract, heart, and peripheral vagal afferents[48]. Therefore, the behavioral effects observed in human studies may not be due to central brain modulation at all, but rather peripheral autonomic nervous system activation that alters subjective states[48]. This pharmacokinetic reality necessitates that all future intranasal studies include intravenous control groups to definitively separate peripheral autonomic effects from central cognitive effects[50].

Vasopressin: Sex-Specific Social Coding

Vasopressin, a neuropeptide closely related to oxytocin, plays a regulatory role in territoriality, pair-bonding, and stress processing. A foundational study by Thompson et al. (2006, $N = 122$; 58 males, 64 females) demonstrated that vasopressin has highly sexually dimorphic effects on social communication[52].

Following double-blind intranasal administration of 40 IU of vasopressin versus saline, men exhibited increased agonistic (hostile/threatening) facial motor patterns and decreased their perception of friendliness in the faces of other men[52]. Conversely, in women, vasopressin stimulated affiliative (friendly/approach) facial motor patterns and increased the perception of friendliness in same-sex faces[52]. These data suggest that identical neuropeptides are differentially routed through male and female neural architectures, likely mediated by varying vasopressin 1a receptor (V1aR) distributions mapped by divergent evolutionary pressures relating to male-male territorial competition and female-female social cohesion[53].

Cortisol and the Sexually Dimorphic Stress Response

Cortisol, the primary glucocorticoid end-product of the HPA axis, governs the mobilization of

metabolic resources in response to threat. While baseline cortisol levels do not differ drastically by sex, the *type* of environmental trigger required to elicit a maximal cortisol spike exhibits notable statistical sexual dimorphism.

In a highly cited study by Stroud, Salovey, and Epel (2002) (N = 50; 24 men, 26 women), healthy volunteers were subjected to two different types of laboratory stress: an achievement stressor (mathematical and verbal challenges) and a social rejection stressor (exclusion by confederates during conversation)[57]. While men and women did not differ in their subjective, self-reported feelings of stress or negative mood, their physiological biomarkers diverged sharply[57]. Men exhibited significantly greater cortisol reactivity to achievement challenges, whereas women exhibited significantly greater cortisol reactivity to social rejection challenges[57].

This suggests that the male HPA axis may be uniquely tuned to threats against competence and hierarchical status, while the female HPA axis is uniquely tuned to threats against social affiliation and network inclusion[57]. However, it is vital to note the state of replication: while the male bias toward achievement stress is generally robust, subsequent studies utilizing paradigms like Cyberball or the Yale Interpersonal Stressor have produced mixed results when attempting to replicate the female cortisol bias toward social rejection[60]. The mapping of social exclusion to HPA axis activation is complex and heavily moderated by individual traits like shame-proneness, prenatal androgen exposure, and baseline sympathetic tone[60].

Stressor Paradigm	**Primary HPA Axis Responders (Stroud et al., 2002)**	**Replication Status**
Achievement Stress (Math/Verbal Challenge)	Men	Generally Robust
Social Rejection Stress (Exclusion Paradigm)	Women	Mixed / Highly Moderated

Parsing Physiology, Behavior, and Culture

To responsibly interpret behavioral neuroendocrinology, one must strictly differentiate what happens at the physiological level from what manifests at the behavioral and cultural levels.

At the **physiological layer**, mechanisms are deterministic and measurable: the HPG and HPA axes operate via feedback loops, allopregnanolone modulates GABA-A receptors altering chloride ion flux, and estradiol alters localized metabolic activation in the frontal cortex under cognitive load. Hormones act as permissive neuro-modulators; they alter the signal-to-noise ratio in the brain, lowering the threshold for certain responses (e.g., threat detection, status protection) while raising the threshold for others.

At the **behavioral layer**, these physiological nudges result in statistical differences in averages between populations. Because men, on average, have higher baseline testosterone and robust

dynamic testosterone reactivity to competition, they are statistically more likely to engage in overt status-seeking behaviors. However, understanding the difference between group averages and individual variance is paramount. The effect sizes governing hormone-behavior links are generally small to moderate (r = 0.05 to 0.15). This translates to massive overlapping distributions between populations. Knowing an individual's sex, or even drawing their blood to measure their baseline testosterone, provides almost no predictive validity regarding how that specific individual will act in an isolated social encounter.

At the **cultural layer**, biology meets environment. Hormones provide the biological drive (e.g., the drive for status, the fear of social exclusion, the imperative to protect the in-group), but culture writes the script. If a society rewards dominance through physical aggression, testosterone will facilitate aggression. If a society rewards dominance through extreme generosity, philanthropy, or bureaucratic competence, testosterone will facilitate those behaviors. Biology provides the ink; culture writes the story.

Summary of Robust Findings

1. The causal link between baseline or dynamic testosterone and physical aggression in humans is statistically very weak (r < 0.11), and exogenous testosterone administration fails to produce a significant causal main effect on aggression.
2. Testosterone primarily modulates status-seeking motivation, which can manifest as antisocial punishment or prosocial generosity entirely depending on environmental and cultural incentives.
3. Premenstrual Dysphoric Disorder (PMDD) is caused by an abnormal central nervous system sensitivity to the *rate of change* in estradiol and progesterone, not by absolute hormonal imbalances.
4. Allopregnanolone, a progesterone metabolite, modulates GABA-A receptors; impaired plasticity in this system drives luteal-phase affective distress, a pathway successfully targeted by low-dose SSRIs acting as steroidogenic stimulants.
5. Intranasal oxytocin does *not* reliably increase interpersonal trust, representing a major failure of replication in the field when subjected to highly powered, preregistered trials.
6. Oxytocin regulates parochial altruism: it increases cooperative behavior and self-sacrifice toward in-groups while simultaneously heightening defensive aggression and prejudice toward out-groups.
7. Vasopressin triggers sexually dimorphic social responses: increasing agonistic facial expressions in men and affiliative expressions in women.
8. Men tend to show greater physiological cortisol reactivity to achievement-based stress, whereas women often show higher reactivity to social rejection, though individual variation is vast and replication is mixed.
9. Baseline hormone levels are exceedingly poor predictors of individual behavior; dynamic fluctuations in response to specific environmental cues are vastly more relevant.
10. The effect sizes governing hormone-behavior links are generally small, resulting in highly overlapping behavioral distributions between men and women that prohibit individual stereotyping.

Contested or Open Questions

- **The Blood-Brain Barrier Dilemma:** Does intranasally administered oxytocin or vasopressin actually reach the central nervous system in sufficient quantities to alter behavior, or are observed behavioral effects artifacts of peripheral autonomic activation?
- **The Dual-Hormone Hypothesis:** Does baseline cortisol truly suppress the behavioral effects of testosterone, or are the meta-analytic effect sizes (r = -0.061) too small to be practically meaningful in real-world human interactions?
- **Exogenous vs. Endogenous Paradigms:** Why do large-scale, preregistered administrations of exogenous testosterone (e.g., 1,000+ participants) routinely fail to replicate the behavioral changes observed in smaller correlational studies of endogenous testosterone?
- **RMET and Empathy:** Does testosterone have any true causal impact on cognitive empathy, or were early positive findings supporting the "Extreme Male Brain" theory entirely the result of underpowered samples and publication bias?
- **Cortisol and Social Rejection:** Is the female-biased cortisol response to social rejection a robust biological reality, or is it heavily confounded by experimental design, baseline sympathetic tone, and cultural context?

Most Important Sources to Read in Full

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Implications for Living Together

The naturalistic fallacy assumes that because a behavior is biologically rooted or evolutionarily ancient, it is morally good or socially desirable. We must explicitly reject this premise. The fact that oxytocin naturally drives parochial altruism—in-group favoritism and out-group hostility—does not mean tribal prejudice is a social good; rather, it highlights an ancient biological bias that modern, multicultural societies must actively consciously design institutions to override.

For couples, families, and organizations, understanding the endocrinology of emotion fosters structural empathy rather than biological determinism. Knowing that PMDD is a genuine neurobiological vulnerability to hormonal transitions (a receptor sensitivity issue)—not a psychological failing—allows families and clinicians to implement targeted, forgiving, and biologically informed interventions without assigning blame. Knowing that the male stress response is highly tuned to achievement and competence allows couples to understand why professional failures may trigger profound, disproportionate withdrawal or irritability in male partners, reframing the conflict from one of personal neglect to one of physiological stress reactivity.

Ultimately, recognizing that testosterone drives *status-seeking* rather than purely *violence* provides a powerful lever for organizational and societal design. Societies and corporations that construct hierarchies where status is awarded for mentorship, ethical conduct, and cooperative success will successfully co-opt the biological drive for dominance, channeling human neuroendocrinology toward the common good. We are not slaves to our hormones; our hormones are metabolic engines waiting for culture to provide the steering wheel.

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