# Pot Is Hot — What You Need to Know

## Cannabinoid-Pharmaceutical Interactions

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*Cannabis samples being prepped at Sonoma Lab Works for analysis of cannabinoids, terpenes, pesticides and residual solvents.*

Interactions between medications are very common, especially in elderly populations that medicate for pain, diabetes and high cholesterol. The geriatric population is also the fastest-growing group of medical cannabis users. Cannabis has demonstrated efficacy in treating pain, and some phytocannabinoids (pCBs) have been suggested for various metabolic conditions.[1-3] Thus it is important to understand how cannabinoids can interact with common pharmaceuticals, both to predict and prevent negative interactions, while taking advantage of situations where cannabis and pharmaceuticals act synergistically.

Drug interactions can be both useful and dangerous. A drug that potentiates an opiate, for example, may increase the painkilling effect, but could also increase the likelihood of overdose. Or a second analgesic could allow the dose of an opiate to be reduced, which would slow tolerance and decrease other side effects.

But understanding all the convergent biological pathways of two drugs is difficult. Examining the metabolic interactions between drugs is one way to generically predict drug interactions: since more than half of all pharmaceuticals are metabolized by a family of enzymes called cytochrome P450 (CYP), knowing how cannabinoids affect CYPs provides a good first approximation to pCB-drug interactions. In general, inhibiting the CYPs that metabolize a pharmaceutical will increase its blood concentration, leading to an increase in both effects and toxicity. But for prodrugs—which are metabolized into the active compound—inhibition of metabolism will *decrease* both the desired and adverse effects. And the interaction can change from inhibition to activation with different drugs.[4] Due to complications like these, it is much easier to predict whether drug interactions are likely than to predict their exact effect.

This review will describe potential cannabinoid-drug interactions in the context of treating pain (with opiates and non-steroidal anti-inflammatory drugs) and metabolic disorders (using insulin, warfarin and statins). Owing to the highly complicated role of cannabinoids in the cardiovascular system—with at least four cannabinoid-like receptors initiating changes in the vasculature, multiple phases to the effects, and opposing effects under normal, stressed and pathological conditions—cannabinoid interactions with drugs used to treat hypertension are beyond the scope of this article.

### The Endocannabinoid System

The endocannabinoid system comprises the two known cannabinoid receptors—CB1 and CB2—as well as their endogenous lipid agonists, the enzymes that break down these agonists, and the transport molecules that shuttle them through the cell. CB1 is the most prevalent G-protein-coupled receptor in the brain; its primary function is to inhibit GABAergic and glutamatergic neurons after they release their respective neurotransmitters. Neural CB1 reduces pain and is required for extinguishing

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fearful memories. CB1 is also broadly distributed in the body, particularly the liver and adipose tissue, where it generally promotes the synthesis of fat. The CB2 receptor is primarily expressed on immune cells where it inhibits the inflammatory response. In disease, overactive endocannabinoid signaling can contribute to fibrosis and insulin resistance. Endocannabinoid deficiencies have been associated with fibromyalgia and autoimmune disorders, among others.

## Cytochrome P450

Cytochrome P450 (CYP) are nonspecific enzymes that oxidize a variety of molecules, making the molecules more water-soluble and easier for the kidneys to filter. CYPs are generally concentrated in the liver. Cannabidiol (CBD), a non-euphoric cannabis component, inhibits CYPs 1A1, 2B6, 2C9, 2C19, 3A4 and 3A5 with submicromolar potency, and can increase the activity of CYPs 2B10 and 2B13.[5-9] Tetrahydrocannabinol (THC; the main psychoactive component of cannabis) is an equally potent inhibitor of CYP2C9, and weakly inhibits other CYPs. Drugs metabolized by these CYP enzymes may have altered plasma concentrations, and this should be monitored closely. But clinically relevant changes in drug metabolism due to CBD are usually seen with high doses of pure CBD.[10-12] Interactions are more likely to occur because of convergent biological pathways.

## Pain Medications

***NSAIDs:*** Nonsteroidal anti-inflammatory drugs work primarily by inhibiting cyclooxygenase 2 (COX2). COX2 produces prostaglandins—a type of inflammatory lipid—from arachidonic acid and endocannabinoids. By inhibiting COX2, NSAIDs reduce inflammation and promote activity at cannabinoid receptors, which appears to be one of their mechanisms of action.[13] This stimulatory influence on the endocannabinoid system suggests potential interactions with cannabis. NSAIDs are metabolized primarily by CYP2C9, which indicates that THC and CBD could decrease the metabolism of NSAIDs and increase their side effects.

But interactions within the endocannabinoid system are likely more important. Both THC and CBD can increase the synaptic concentration of anandamide, a major endocannabinoid.[14] Since COX2 is membrane-bound, this could increase the role of COX2 in metabolizing endocannabinoids. In combination, phytocannabinoids and NSAIDs may lead to a superadditive or synergistic effect on cannabinoid signaling. The subsequent activation of CB1 and CB2 receptors confers analgesic and anti-inflammatory effects. In short, cannabinoids are likely to synergize with NSAIDs, potentiating the analgesia while minimally impacting the gastric side effects.

*Gas chromatography is used to analyze terpenes and residual solvents in cannabis extracts.*

Ibuprofen appears to modify endocannabinoid signaling even more directly. In addition to inhibiting COX2, ibuprofen or its metabolites inhibit fatty acid amide hydrolase (FAAH), the main enzyme responsible for breaking down anandamide.[15] The increase in cannabinoid signaling by these three mechanisms is unlikely to exacerbate the side effects of ibuprofen—which are largely due to COX1 inhibition—but it should potentiate their anti-inflammatory and painkilling effects. Unfortunately, this interaction has not been studied in detail—to the author's knowledge no studies have examined simultaneous use of phytocannabinoids and NSAIDs for analgesia. But promising studies have shown synergy when anandamide is administered with NSAIDs.[16-17]

***Opiates:*** Opiates are very powerful analgesics but are complicated by tolerance, dependence and withdrawal. They act primarily on μ-opioid receptors (μORs) in the spinal cord, brain and brainstem. The latter is responsible for respiratory depression during overdose. Generally, opiates are metabolized by CYPs 3A4 and 2D6.[18] High doses of CBD could interact with opiates via CYP3A4, but this has not been seen clinically. Oral CBD (400-800 mg) administered with intravenous fentanyl did not increase adverse effects.[19] The same lack of effect has been shown for morphine when THC-rich cannabis is vaporized.[10]

Endogenously, cannabinoids and opioids modulate each other. CB1 and μOR receptors can dimerize to convey analgesic signals.[20] The lack of CB1 receptors in the brainstem suggests the possibility of potentiating opiate analgesia without influencing the lethal threshold—in other words, CB1 agonists (such as THC) can widen the therapeutic window of opiates.[21] CB1 agonism can also potentiate the addictive nature of opiates, according to some research.[22] But recent epidemiological data have lessened this concern: prescription opiate use and overdose deaths have significantly decreased in states with medical cannabis laws.[23-24]

The most promising cannabinoid-opiate interactions appear to be between CBD and opiates. CBD reduces cue-induced heroin-seeking, likely through its modulation of dopamine and serotonin.[25-26] CBD—and to a lesser extent THC—are negative allosteric modulators of μ- and δ-opioid receptors, meaning they decrease the activity of opiates at these receptors.[27-28] Both THC and CBD can reduce opiate withdrawal in animals.[29-30] Other ways of either antagonizing or augmenting the endocannabinoid system have also shown promise in reducing opiate withdrawal and tolerance.[31-33]

Our understanding of the interplay between cannabinoids and opiates is still developing, but the clinical data demonstrate significant synergy between the two,

with minimal changes in opiate metabolism and toxicity. THC appears to synergize most with the painkilling effect of opiates, while CBD is most promising for reducing withdrawal and dependence. Hence, cannabinoids are likely to potentiate opiates, decreasing pain while minimizing risks associated with tolerance, dependence and overdose. Not all interactions will be positive, but the potential is there, and dramatic problems appear unlikely.

## Metabolic Syndromes

***Insulin:*** There is strong preclinical evidence that cannabinoids influence glucose and insulin sensitivity, which could have a serious impact on patients with type 1 or type 2 diabetes, though the effect will depend on which cannabinoids are taken.[34] Insulin sensitivity will likely be impaired by psychoactive constituents of cannabis like THC, while cannabinoids including CBD and tetrahydrocannabivarin (THCV) may increase sensitivity to insulin. CB1 activation is part of a feedback mechanism that reduces the body's response to glucose and insulin.[35-36] Some studies, although fewer, show the opposite.[2,37] One CB1 antagonist, Rimonabant, was briefly approved in Europe for treating obesity, but severe psychiatric complications (depression and suicidal behavior) forced its removal from the market.

*Gel caps being formulated with specific concentrations of THC and CBD from $CO_2$-extracted cannabis oil.*

Epidemiological data, however, complicates the picture. Cannabis use is associated with an overall decrease of metabolic syndromes.[1] Moreover, while there is an increased prevalence of prediabetes among cannabis users, there is no change or a lower incidence of diabetes compared to the general population. It is not clear if this is due to uncontrolled confounding factors or if the effect of CB1 activation changes between healthy and insulin insensitive individuals. It is possible that the endocannabinoid system buffers insulin sensitivity rather than strictly inhibiting it.[38]

***Statins:*** Statins reduce the synthesis of cholesterol by blocking HMG-CoA reductase, an important early step in the production of cholesterol by the liver. This effect is not necessarily specific to low-density lipoprotiens. The metabolism of statins is less general than for other drugs mentioned here. Statins are metabolized by CYPs 3A4/5, 2C8/9/19 and 2D6, indicating that phytocannabinoids could change statin metabolism. Prodrugs like simvastatin and lovastatin require metabolism to become active. The more hydrophilic statins (e.g., pravastatin) are excreted by the kidneys with minimal metabolism by CYPs, so these statins are unlikely to be affected by cannabinoids. Cannabinoids are known to be involved in cholesterol metabolism, heart disease and mitochondrial function, which raises the possibility of interactions with statins by non-metabolic means.[39-40] CB1 activation may even inhibit HMG-CoA reductase, although this was only shown in cancer cells.[41]

The major interactions between statins and phytocannabinoids will likely be on cannabinoid function. Cholesterol levels are intimately involved in CB1 receptor function. CB1 has multiple binding sites for cholesterol, which influences many aspects of its signaling.[42-43] The cholesterol precursor pregnenalone decreases CB1 activity.[44] Cholesterol similarly inhibits CB1, but it also directs CB1 to its proper location in neurons.[42-43,45-46] If the latter effect is more dominant, cannabinoids—especially psychoactive cannabinoids—could become less effective in patients taking statins. This would be relevant for the treatment of multiple sclerosis, pain, cachexia and epilepsy, among others (i.e., conditions for which activation of CB1 is important).

But if the former effect of cholesterol-inhibiting CB1 is dominant, then statins may amplify the effect of cannabinoids, resulting in increased side effects like anxiety. These changes will be particularly relevant in patients taking THC, which directly activates CB1 receptors. Cannabinoids also exert effects through changes in membrane fluidity and permeability, which will certainly be altered if cholesterol levels are decreased. Patients taking cannabinoids who begin treatment with statins should be warned that the effective dose of cannabinoids will likely change. (Note that there is no established "normal" dose of cannabinoids. Doses of THC range from roughly 1 to 50 mg, and are dependent on a patient's condition, tolerance, experience and comfort with the psychoactivity of THC. If a patient has found an effective dose of cannabinoids, statins could shift this dose in either direction.)

***Warfarin:*** Warfarin is one of the most widely used blood thinners and is primarily inactivated by CYP2C9. Common mutations in CYP2C9 reduce its activity to less than half of normal, which may contribute to the difficulty of dosing warfarin; over a third of all patients who take warfarin end up in the emergency room before an optimal dose is found, according to a 2008 report.[47] THC and CBD can both inhibit CYP2C9, and hence amplify warfarin's effects. This has been demonstrated in a case study as well as preclinical work.[48] Doctors should be cautious about mixing cannabinoids with warfarin, although reducing the dose of warfarin should be enough to prevent adverse effects.

## Cannabinoid-Cannabinoid Interactions

It would be inappropriate to address cannabinoid-drug interactions without mentioning the influence of many cannabinoid and terpenoid compounds on each other, sometimes called the "entourage" effect.[49-50] Cannabis is a plant, not a drug. Different varietals (i.e., strains) and

growing practices lead to plants with very different compositions and effects. Studies have shown that THC and CBD potentiate many of each other's medical effects while mitigating others.[51-52]

CBD isolates have narrower therapeutic windows and generally require higher doses than whole-plant preparations.[53-54] For example, GW Pharmaceuticals' Epidiolex is a pure CBD sublingual tincture that has been tested in clinical trials for certain forms of epilepsy. While it has been effective in many patients, it requires doses of 5–50 mg/kg/day, which is up to 1.2 grams of CBD for a 50-pound child.[12] With such enormous doses, drug interactions become very likely.

By comparison, artisanal cannabis preparations usually require 1–100 mg of cannabinoids.[55-56] In many ways, the entourage effect is a microcosm of drug interactions on the whole. Without a detailed understanding of the medicine being used, the variety of chemicals can lead to inconsistent results and may reduce medical efficacy or potentiate side effects. Or interactions between drugs can be exploited to mitigate each other's side effects while synergistically improving a patient's quality of life. ◇

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## References


1. National Academies of Sciences, Engineering and Medicine, "The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research," *The National Academies Press* (2017).
2. Jadoon KA, et al, "Efficacy and safety of cannabidiol and tetrahydrocannabivarin on glycemic and lipid parameters in patients with type 2 diabetes: a randomized, double-blind, placebo-controlled, parallel group pilot study," *Diabetes Care,* 39(10):1777-86 (2016).
3. Wargent ET, et al, "The cannabinoid (9)-tetrahydrocannabivarin (THCV) ameliorates insulin sensitivity in two mouse models of obesity," *Nutr Diabetes,* 3:68 (2013).
4. Egnell AC, et al, "Predictive models of CYP3A4 heteroactivation: in vitro-in vivo scaling and pharmacophore modeling." *J Pharmacol Exp Ther,* 312(3):926-37 (2005).
5. Yamaori S, et al, "Protent inhibition of human cytochrome P450 3A isoforms by cannabidiol: role of phenolic hydroxyl groups in the resorcinol moiety," *Life Sci,* 88(15-16):730-6 (2011).
6. Bornheim LM, et al, "Characterization of cannabidiol-mediated cytochrome P450 inactivation," *Biochem Pharmacol,* 45(6):1323-31 (1993).
7. Yamaori S, et al, "Structural requirements for potent direct inhibition of human cytochrome P450 1A1 by cannabidiol: role of pentylresorcinol moiety," *Biol Pharm Bull,* 36(7):1197-203 (2013).
8. Jiang R, et al, "Cannabidiol is a potent inhibitor of the catalytic activity of cytochrome P450 2C19," *Drug Metab Pharmacokinet,* 28(4):332-8 (2013).
9. Yamaori S, et al, "Comparison in the in vitro inhibitory effects of major phytocannabinoids and polycyclic aromatic hydrocarbons contained in marijuana smoke on cytochrome P450 2C9 activity," *Drug Metab Pharmacokinet,* 27(3):294-300 (2012).
10. Abrams DI, et al, "Cannabinoid-opioid interaction in chronic pain," *Clin Pharmacol Ther,* 90(6):844-51 (2011).
11. Geffrey AL, et al, "Drug-drug interaction between clobazam and cannabidiol in children with refractory epilepsy," *Epilepsia,* 56(8):1246-51 (2015).
12. Gaston TE, et al, "Interactions between cannabidiol and commonly used antiepileptic drugs," *Epilepsia,* Epub ahead of print – DOI: 10.1111/epi.13852 (2017).
13. Silva LC, et al, "Participation of cannabinoid receptors in peripheral nociception induced by some NSAIDs," *Braz J Med Biol Res,* 45(12):1240-3 (2012).
14. Deutsch DG, "A Personal Retrospective: Elevating Anandamide (AEA) by Targeting Fatty Acid Amide Hydrolase (FAAH) and the Fatty Acid Binding Proteins (FABPs)," *Front Pharmacol,* 7:370 (2016).
15. Duggan KC, et al, (R)-Profens are substrate-selective inhibitors of endocannabinoid oxygenation by COX-2," *Nat Chem Biol,* 7(11):803-9 (2011).
16. Guindon J, et al, "Synergistic antinociceptive effects of anandamide, an endocannabinoid, and nonsteroidal anti-inflammatory drugs in peripheral tissue: a role for endogenous fatty-acid ethanolamides?", *Eur J Pharmacol,* 550 (1-3):68-77 (2006).
17. Guindon J, et al, "Local interactions between anandamide, an endocannabinoid, and ibuprofen, a nonsteroidal anti-inflammatory drug, in acute and inflammatory pain," *Pain,* 121 (1-2):85-93 (2006).
18. Smith HS, "Opioid metabolism," *Mayo Clin Proc,* 84(7):613-24 (2009).
19. Manini AF, et al, "Safety and pharmacokinetics of oral cannabidiol when administered concomitantly with intravenous fentanyl in humans," *J Addict Med,* 9(3):204-10 (2015).
20. Hojo M, et al, "mu-Opioid receptor forms a functional heterodimer with cannabinoid CB1 receptor: electrophysiological and FRET assay analysis," *J Pharmacol Sci,* 108(3):308-19 (2008).
21. Cooper ZD et al, "Oxycodone's effects on cannabis-induced analgesia and subjective drug ratings," presented at the 2016 International Cannabinoid Research Society.
22. Spano MS, et al, "Cannabinoid-opioid interactions in drug discrimination and self-administration: effect of maternal, postnatal, adolescent and adult exposure to the drugs," *Curr Drug Targets,* 11(4):450-61 (2010).
23. Bradford AC, Bradford WD, "Medical Marijuana Laws Reduce Prescription Medication Use In Medicare Part D," *Health Aff,* 35(7):1230-6 (2016).
24. Corroon JM, et al, "Cannabis as a substitute for prescription drugs—a cross-sectional study," *J Pain Res*, 10:989-998 (2017).
25. Ren Y, et al, "Cannabidiol, a nonpsychotropic component of cannabis, inhibits cue-induced heroin seeking and normalizes discrete mesolimbic neuronal disturbances," *J Neurosci*, 29(47):14764-9 (2009).
26. Katsidoni V, et al, "Cannabidiol inhibits the reward-facilitating effect of morphine: involvement of 5-HT1A receptors in the dorsal raphe nucleus," *Addict Biol*, 18(2):286-96 (2013).
27. Kathmann M, et al, "Cannabidiol is an allosteric modulator at mu- and delta-opioid receptors," *Naunyn Schmiedebergs Arch Pharmacol,* 372(5):354-61 (2006).
28. Vaysse PJ, et al, "Modulation of rat brain opioid receptors by cannabinoids," *J Pharmacol Exp Ther,* 241(2):534-9 (1987).
29. Chesher GB, Jackson DM, "The quasi-morphine withdrawal syndrome: effect of cannabinol, cannabidiol and tetrahydrocannabinol," *Pharmacol Biochem Behav*, 23(1):13-5 (1985).
30. Hurd YL, et al, "Early phase in the development of cannabidiol as a treatment for addiction: opioid relapse takes initial center stage," *Neurotherapeutics*, 12(4):807-15 (2015).
31. Wills KL, Parker LA, "Effect of pharmacological modulation of the endocannabinoid system on opiate withdrawal: a review of the preclinical animal literature," *Front Pharmacol,* 7:187 (2016).
32. Wills KL, et al, "Double dissociation of monoacylglycerol lipase inhibition and CB1 antagonism in the central amygdala, basolateral amygdala, and the interoceptive insular cortex on the affective properties of acute naloxone-precipitated morphine withdrawal in rats," *Neuropsychopharmacology,* 41(7):1865-73 (2016).
33. Wills KL, et al, "CB1 antagonism: interference with affective properties of acute naloxone-precipitated morphine withdrawal in rats," *Psychopharmacology,* 231(22):4291-300 (2014).
34. Argueta DA, DiPatrizio NV, "Peripheral endocannabinoid signaling controls hyperphagia in western diet-induced obesity," *Physiol Behav,* 171:32-39 (2017).
35. Lindborg KA, et al, "Effects of in vitro antagonism of endocannabinoid-1 receptors on the glucose transport system in normal and insulin-resistant rat skeletal muscle," *Diabetes Obes Metab,* 12(8):722-30 (2010).
36. Araújo JR, et al, "Modulation of glucose uptake in a human choriocarcinoma cell line (BeWo) by dietary bioactive compounds and drugs of abuse," *J Biochem,* 144(2):177-86 (2008).
37. Miederer I, et al, "Effects of tetrahydrocannabinol on glucose uptake in the rat brain," *Neuropharmacology,* 117:273-281 (2017).
38. Lau BK, et al, "Endocannabinoid modulation of homeostatic and non-homeostatic feeding circuits," *Neuropharmacology,* 124:38-51 (2017).
39. Lipina C, et al, "Mitochondria: a possible nexus


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**References,** *continued from page 36*

for the regulation of energy homeostasis by the endocannabinoid system?", *Am J Physiol Endocrinol Metab*, 307(1):1-13 (2014).

40. Rimmerman N, et al, "The non-psychoactive plant cannabinoid, cannabidiol affects cholesterol metabolism-related genes in microglial cells," *Cell Mol Neurobiol,* 31(6):921-30 (2011).
41. Laezza C, et al, "Inhibition of 3-hydroxy-3-methylglutaryl-coenzyme A reductase activity and of Ras farnesylation mediate antitumor effects of anandamide in human breast cancer cells," *Endocr Relat Cancer,* 17(2):495-503 (2010).
42. Oddi S, et al. "Palmitoylation of cysteine 415 of CB1 receptor affects ligand-stimulated internalization and selective interaction with membrane cholesterol and caveolin 1," *Biochim Biophys Acta,* 1862(5):523-532 (2017).
43. Oddi S, et al, "Functional characterization of putative cholesterol binding sequence (CRAC) in human type-1 cannabinoid receptor," *J Neurochem,* 116(5):858-65 (2011).
44. Vallée M, et al, "Pregnenolone can protect the brain from cannabis intoxication," *Science,* 343(6166):94-8 (2014).
45. Stornaiuolo M, et al, "Endogenous vs exogenous allosteric modulators in GPCRs: a dispute for shuttling CB1 among different membrane microenvironments," *Sci Rep,* 5:15453 (2015).
46. Hering H, et al, "Lipid rafts in the maintenance of synapses, dendritic spines, and surface AMPA receptor stability," *J Neurosci* 23(8):3262-71 (2003).
47. Carlson B, "Declaring war on warfarin misdosing," *Biotechnology Healthcare,* 5(2):54-55 (2008).
48. Yamreudeewong W, et al, "Probable interaction between warfarin and marijuana smoking," *Ann Pharmacother,* 43(7):1347-53 (2009).
49. Russo EB, "Taming THC: Potential cannabis synergy and phytocannabinoid-terpenoid entourage effects," *Br J Pharmacol,* 163(7):1344-64 (2011).
50. Russo E, Guy GW, "A tale of two cannabinoids: The therapeutic rationale for combining tetrahydrocannabinol and cannabidiol," *Med Hypotheses,* 66(2):234-46 (2006).
51. Britch SC, et al, "Cannabidiol-9-tetrahydrocannabinol interactions on acute pain and locomotor activity," *Drug Alcohol Depend,* 175:187-197 (2017).
52. Todd SM, et al, "Interactions between cannabidiol and 9-THC following acute and repeated dosing: rebound hyperactivity, sensorimotor gating and epigenetic and neuroadaptive changes in the mesolimbic pathway," *Eur Neuropsychopharmacol,* 27(2):132-145 (2017).
53. Gallily R, et al, "Overcoming the bell-shaped dose-response of cannabidiol by using cannabis extract enriched in cannabidiol," *Pharmacology & Pharmacy,* 6:75-85 (2015).
54. De Petrocellis L, et al, "Effects of cannabinoids and cannabinoid-enriched cannabis extracts on TRP channels and endocannabinoid metabolic enzymes," *Br J Pharmacol,* 163(7):1479-94 (2011).
55. Goldstein, Bonni. *Cannabis Revealed: How the world's most misunderstood plant is healing everything from chronic pain to epilepsy*, Goldstein (2016).
56. Sulak D, et al, "The current status of artisanal cannabis for the treatment of epilepsy in the United States," *Epilepsy Behav,* 70:328-333 (2017).