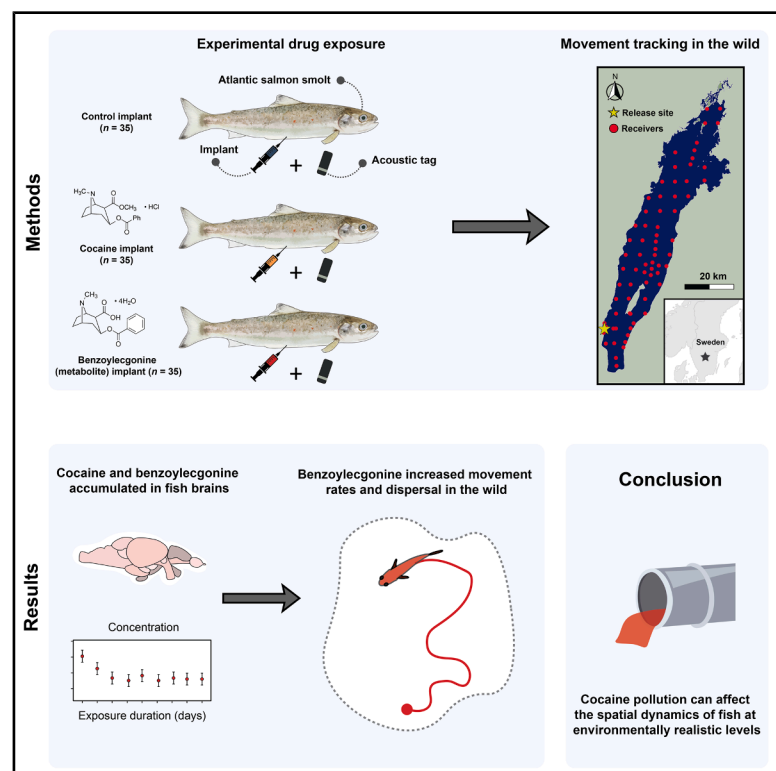


Current Biology

Cocaine pollution alters the movement and space use of Atlantic salmon (*Salmo salar*) in a large natural lake

Graphical abstract



Authors

Jack A. Brand, Daniel Palm, Daniel Cervený, ..., Bryan W. Brooks, Tomas Brodin, Michael G. Bertram

Correspondence

jack.brand@slu.se (J.A.B.), michael.bertram@slu.se (M.G.B.)

In brief

Brand et al. show that environmentally realistic benzoyllecgonine exposure increases movement and dispersal of Atlantic salmon smolts in a natural lake. Exposed fish swam and dispersed farther than controls, demonstrating that cocaine-derived pollutants can alter fish spatial ecology in the wild.

Highlights

- Cocaine metabolite benzoyllecgonine increased the movement of juvenile Atlantic salmon
- Exposed fish swam up to 1.9 times farther per week than control fish
- Benzoyllecgonine increased dispersal by up to 12.3 km
- Cocaine-associated pollution altered salmon spatial ecology in a natural lake



Article

Cocaine pollution alters the movement and space use of Atlantic salmon (*Salmo salar*) in a large natural lake

Jack A. Brand,^{1,2,10,*} Daniel Palm,¹ Daniel Cervený,^{1,3} Marcus Michelangeli,^{1,4} Aneesh P.H. Bose,^{1,5} Erin S. McCallum,¹ Gustav Hellström,¹ Jerker Fick,⁶ Bryan W. Brooks,⁷ Tomas Brodin,¹ and Michael G. Bertram^{1,8,9,*}

¹Department of Wildlife, Fish, and Environmental Studies, Swedish University of Agricultural Sciences, SE-907 36 Umeå, Sweden

²Institute of Zoology, Zoological Society of London, London NW1 4RY, UK

³South Bohemian Research Center of Aquaculture and Biodiversity of Hydrocenoses, Faculty of Fisheries and Protection of Waters, University of South Bohemia in Ceske Budejovice, 389 25 Vodnany, Czech Republic

⁴Australian Rivers Institute, Griffith University, Nathan, QLD 4111, Australia

⁵Behavioral Evolution Research Group, Max Planck Institute of Animal Behavior, 78467 Konstanz, Germany

⁶Department of Chemistry, Umeå University, SE-901 87 Umeå, Sweden

⁷Department of Environmental Science, Baylor University, Waco, TX 76798-7266, USA

⁸Department of Zoology, Stockholm University, SE-114 18 Stockholm, Sweden

⁹School of Biological Sciences, Monash University, Clayton, VIC 3800, Australia

¹⁰Lead contact

*Correspondence: jack.brand@slu.se (J.A.B.), michael.bertram@slu.se (M.G.B.)

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SUMMARY

Cocaine and its metabolites are increasingly being detected in aquatic environments worldwide. While previous research has demonstrated that these substances can affect brain function and behavior in wildlife, this research has exclusively been conducted under artificial laboratory conditions. How cocaine pollution affects animal behavior in the wild is, thus, unknown. Here, we combine slow-release chemical implants with acoustic telemetry tracking to reveal how environmentally realistic levels of cocaine and its main metabolite, benzoylecgonine, affect the movement of Atlantic salmon (*Salmo salar*) smolts in a large natural lake (Lake Vättern, Sweden). Benzoylecgonine exposure increased weekly movement rates of fish in the wild, with exposed fish swimming up to ~1.9 times farther per week relative to controls. In addition, benzoylecgonine-exposed fish dispersed up to ~12.3 km farther than control conspecifics. These results indicate that cocaine-derived pollutants can alter fish spatial ecology, potentially influencing habitat use, trophic interactions, and population-level dispersal patterns in natural ecosystems.

INTRODUCTION

Illicit drug pollution poses an increasing risk to ecosystem function and human health.^{1,2} An estimated 292 million people worldwide used illicit substances in 2022 alone,³ with many of these compounds being excreted and subsequently detected in aquatic environments due to insufficient removal during wastewater treatment, which is lacking in many locations around the world.^{2,4} Once in the environment, these substances can pose a particular threat to non-target wildlife due to their potency at low concentrations and their ability to interact with evolutionarily conserved neurological pathways.^{1,2,5} Moreover, with the global use of illicit drugs increasing by ~20% over the last decade,³ the environmental impact of these substances is likely to grow.⁶

Illicit drugs and their metabolites are known to cause sublethal effects in aquatic organisms at environmentally relevant concentrations.² This is especially true of behavioral traits, as illicit substances often alter brain functioning and behavior.^{2,7–9} Such behavioral alterations can influence organismal survival and reproductive success,¹⁰ with potential consequences for

species ecology and evolution.¹¹ Despite this, a recent systematic map of behavioral ecotoxicology revealed that among 1,739 unique species-by-compound combinations studied since 1974, only ~5.1% involved illicit drugs¹²—exposing a major gap in our understanding of their ecological effects.

Cocaine is one of the most commonly detected illicit substances in aquatic environments worldwide.² For instance, analysis of treated wastewater effluent discharging into Australian rivers reported maximum concentrations of 2,990 and 21,570 ng L^{−1} for cocaine and its main urinary metabolite, benzoylecgonine, respectively.¹³ A recent meta-analysis also reported mean global surface water concentrations of 105.1 ng L^{−1} (±431.3; maximum = 5,896 ng L^{−1}) and 257.4 ng L^{−1} (±1,074.4; maximum = 3,582 ng L^{−1}) for cocaine and benzoylecgonine, respectively.¹⁴ Though studies on bioaccumulation are limited, both compounds have been detected in wild aquatic organisms. For example, muscle samples collected from wild Brazilian sharpnose sharks (*Rhizoprionodon lalandii*) contained a maximum of 107.5 ng g^{−1} of cocaine and 18.7 ng g^{−1} of benzoylecgonine.¹⁵ A broader meta-analysis



also reported mean tissue concentrations of cocaine around 3 ng g^{-1} (range: $0\text{--}30.8 \text{ ng g}^{-1}$) across mussels, macroinvertebrates, and fish sampled from China, the United Kingdom, and the United States of America¹⁴—stressing the prevalence of cocaine pollution in aquatic environments.

Cocaine is a psychomotor stimulant that can accumulate in the brain of exposed organisms and affect monoaminergic systems involved in behavior.¹⁶ For example, dilute concentrations (20 ng L^{-1}) of cocaine were shown to accumulate in the tissues of European eels (*Anguilla anguilla*) after a 1-month exposure, with the highest levels recorded in the brain ($30.50 \pm 0.36 \text{ pg g}^{-1}$), followed by muscle ($20.17 \pm 0.47 \text{ pg g}^{-1}$) and liver ($13.4 \pm 2.17 \text{ pg g}^{-1}$).¹⁷ This exposure increased brain and plasma dopamine levels in the eels,¹⁸ with prior research finding associations between brain dopaminergic activity and fish swimming behavior.^{19,20} Cocaine and its metabolite, benzoylecgonine, have also been shown to affect behavior in aquatic invertebrates: *Daphnia magna* exposed to 50 ng L^{-1} of cocaine swam $\sim 20\%$ faster than controls,²¹ while exposure to $1,000 \text{ ng L}^{-1}$ of benzoylecgonine increased oxidative stress and reduced reproduction.²² Finally, exposure to 500 ng L^{-1} of cocaine increased risk-taking behavior and reduced feeding in red swamp crayfish (*Procambarus clarkii*).⁷ These results emphasize the capacity of cocaine and its metabolites to affect the behavior of aquatic organisms at environmentally relevant concentrations.

To date, existing research on the effects of cocaine pollution on aquatic animal behavior has been conducted in controlled laboratory settings, which do not reflect the complexity of natural environments.^{12,23} Indeed, animal behavior is highly sensitive to environmental conditions, with research often finding that behavioral traits measured in the laboratory are not representative of those expressed in more naturalistic settings.^{24–27} Given the prevalence of cocaine in aquatic environments and its ability to alter organismal behavior, there is a pressing need to understand how cocaine pollution may be affecting the behavior and performance of animal populations in the wild.

Here, we conducted a large field experiment in Lake Vättern, Sweden (surface area = $1,912 \text{ km}^2$; maximum depth = 128 m ; Figure 1A), to investigate whether exposure to cocaine and its metabolite benzoylecgonine could affect the movement of Atlantic salmon (*Salmo salar*) smolts in the wild. Atlantic salmon are an ecologically and economically important species that has experienced significant declines in recent years, largely driven by human-induced environmental changes—including chemical pollution.^{28–31} Indeed, analysis of Swedish wastewater effluent within the native distribution of Atlantic salmon revealed maximum discharge rates of approximately 3.6 and 14.1 g day^{-1} of cocaine and benzoylecgonine to aquatic environments, respectively.³² Further, samples of British rivers within the distribution of Atlantic salmon were found to contain a maximum of 17.4 and 72.4 ng L^{-1} of cocaine and benzoylecgonine, respectively,³³ emphasizing the potential threat of cocaine pollution to wild salmon populations. Despite these observations, how these substances affect salmon in the wild is not known.

We experimentally exposed 2-year-old, hatchery-reared Atlantic salmon (hereafter referred to as “salmon”) smolts to cocaine or benzoylecgonine in the field (hereafter referred to as the “cocaine” and “metabolite” treatment groups, respectively), using previously validated slow-release chemical implants.^{34–36}

Treatment groups ($n = 35$ fish per treatment) were administered either a cocaine or metabolite (i.e., benzoylecgonine) implant or an implant containing no drug (i.e., control implant). Following implant administration and recovery, fish were released into the southwestern region of Lake Vättern ($57^\circ 56' 29.47'' \text{ N}$, $14^\circ 7' 35.87'' \text{ E}$), after which their movements were tracked using acoustic telemetry. We first investigated whether exposure to cocaine or its metabolite influenced the estimated survival of smolts in Lake Vättern over our study period, but as there is limited research on illicit drugs and fish in the wild, we had no clear predictions about the direction of this effect. However, given previous research demonstrating the effects of cocaine and its metabolites on brain dopamine levels in fish¹⁸ and movement rates in aquatic organisms,^{7,21,22} we expected that the cocaine- and metabolite-exposed groups would demonstrate increased movement rates and space use compared with the control group.

RESULTS

Apparent survival

We first investigated whether apparent survival time (i.e., number of days between the tagging date of each individual fish and the corresponding final detection within the comprehensive receiver array) differed between exposure treatments, following established approaches.³⁷ This approach offers an approximate estimate of survival (STAR Methods), and hence, we refer to this measure as “apparent survival time.”³⁸ Both the cocaine- and metabolite-treatment groups demonstrated slightly greater apparent survival when compared with control fish (Figure 1B). However, there was substantial uncertainty around the magnitude and direction of these estimates, with all credible intervals (CIs) containing zero (control-cocaine contrast [89% CI] = $-0.29 [-0.68, 0.10]$; control-metabolite contrast [89% CI] = $-0.27 [-0.66, 0.15]$). The median time until 50% of fish from each treatment group were presumed dead was ~ 75 days (89% CI: 58, 99 days) and ~ 73 days (89% CI: 56, 98 days) in the cocaine- and metabolite-treatment groups, respectively, compared with ~ 55 days (89% CI: 43, 74 days) in the control group (Figure 1C). There was no substantial difference in apparent survival between the cocaine- and metabolite-treatment groups (cocaine-metabolite contrast [89% CI] = $0.03 [-0.37, 0.45]$). We restricted subsequent analyses of smolt movement and space use to the first 8 weeks (i.e., 56 days) of tracking, as this is when $\sim 50\%$ of fish in each treatment group were presumed to be alive and when we could be sure that exposed smolts had detectable levels of cocaine and benzoylecgonine in their brain tissue (STAR Methods).

Movement dynamics

Fish from all treatments became less active and more resident over the course of the 8-week study period. Specifically, fish from the control (estimate [89% CI] = $-4.6 [-5.5, -3.7]$), cocaine (estimate [89% CI] = $-3.3 [-4.1, -2.4]$), and metabolite (estimate [89% CI] = $-3.7 [-4.6, -2.8]$) groups all decreased in terms of the number of unique receivers that they were detected on per week over the course of the experiment (Figure 2A; Table S2). However, this decrease in movement was greater in control fish compared with the cocaine-treatment group (control-cocaine

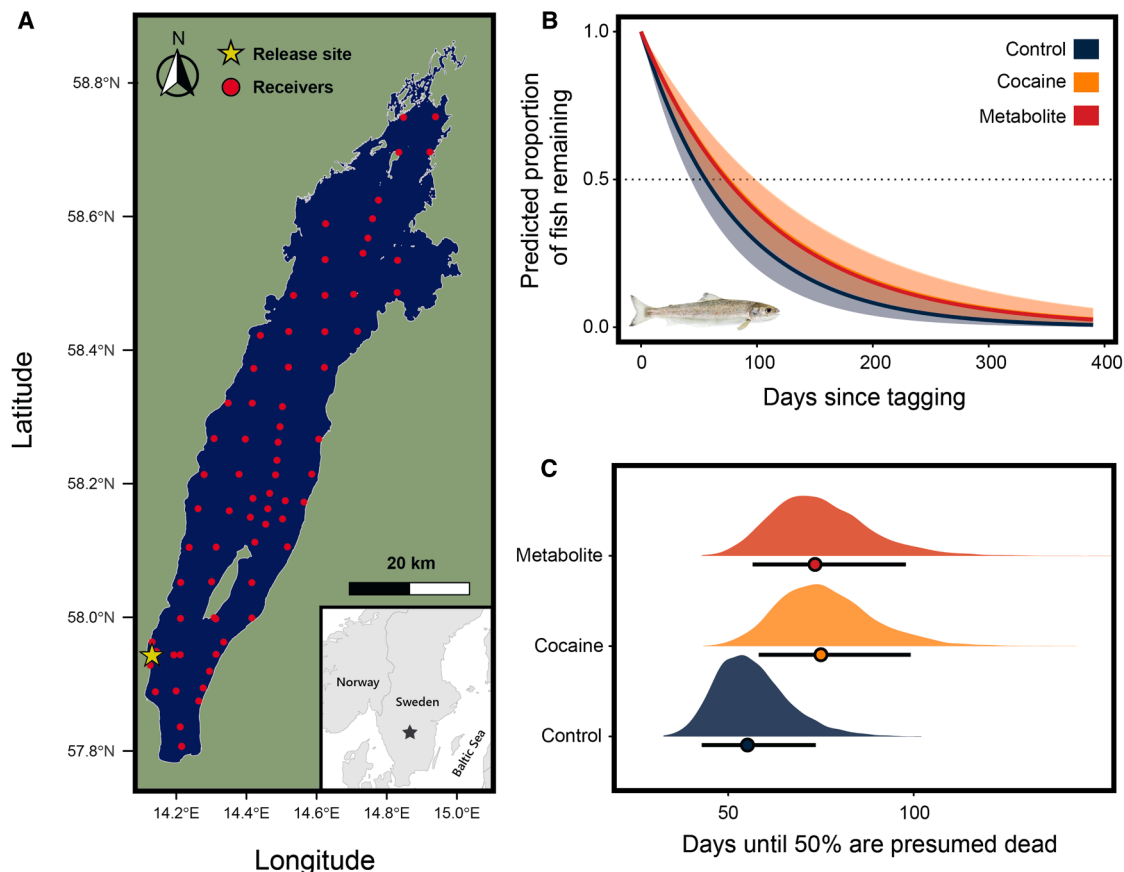


Figure 1. Study site and Atlantic salmon (*Salmo salar*) smolt survival in Lake Vättern

(A) Simplified schematic of the Lake Vättern study site. Acoustic receivers are indicated by red dots, while the release site is denoted by a yellow star in the southwest region. The approximate position of the lake in Sweden is indicated by a black star in the map insert.

(B) Estimates of the proportion of fish remaining (i.e., presumed alive) in the lake for the control (blue), cocaine (orange), and metabolite (red) treatment groups extracted from the Bayesian generalized linear model (GLM). Uncertainty bands denote 89% CIs. Note: both the orange and red lines in the figure overlap (i.e., the cocaine and metabolite groups had similar survival estimates).

(C) Estimated time (in days) until 50% of each treatment group is presumed dead. Point estimates denote posterior medians, while error bars denote 89% CIs. Colored distributions represent the posterior distributions (note: the maxima of the posterior distributions extend beyond the current plot limits). However, the Cartesian coordinates of these plots have been limited to better visualize average treatment differences. Atlantic salmon smolt photo insert credit: Jörgen Wiklund.

See also Table S1.

contrast [89% CI] = -1.37 [-2.62 , -0.18]). There was minimal evidence for any differences in the number of unique receivers that fish were detected on per week over the course of the study in the control and metabolite groups (control-metabolite contrast [89% CI] = -0.94 [-2.25 , 0.29]), or the cocaine and metabolite groups (cocaine-metabolite contrast [89% CI] = 0.42 [-0.84 , 1.64]).

Similarly, all fish in the control (estimated decrease in km [89% CI] = -30.2 [-42.0 , -18.5]), cocaine (estimated decrease in km [89% CI] = -21.1 [-32.9 , -9.6]), and metabolite (estimated decrease in km [89% CI] = -20.0 [-33.9 , -5.6]) groups decreased their total distances swum per week over the course of the 8-week experiment (Figure 2B; Table S3). Although this decreasing trend was greater in the control group compared with the cocaine (control-cocaine contrast [89% CI] = -9.1 [-24.3 , 7.6]) and metabolite (control-metabolite contrast [89% CI] = -10.0 [-28.5 , 7.8]) groups, there was substantial uncertainty

around these estimates, with CIs overlapping zero. While there were few differences in swimming activity among the treatment groups at the beginning of the study period (Table S3), the marginal differences in the temporal trends for each treatment group resulted in the metabolite group swimming significantly farther per week than the control group in the final month of the study. Specifically, the metabolite-treatment group swam ~ 1.5 times farther per week (~ 12.0 [89% CI: 2.0 , 22.0] km more) than the control group during weeks 5–6 of the tracking period, and this increased to ~ 1.9 times farther per week (~ 13.7 [89% CI: 3.0 , 25.3] km more) than the control group in the final 2 weeks (i.e., weeks 7–8) of the study (Figure 2B). Further, the cocaine group swam ~ 5.3 km [89% CI: -3.3 , 14.5 km] farther per week than the control group in the final 2 weeks of the study period, albeit with significant uncertainty in the effect.

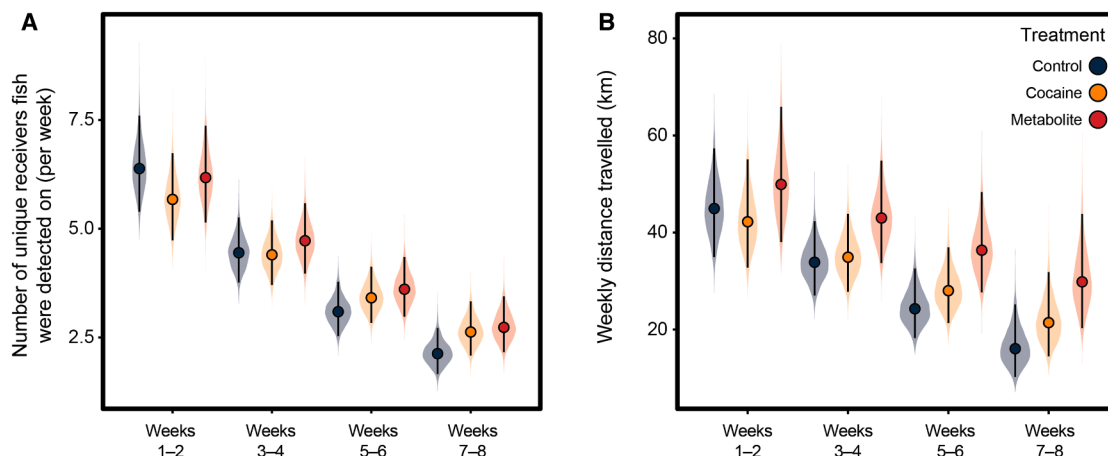


Figure 2. Treatment differences in movement dynamics over the course of the study

(A) Number of unique receivers that fish were detected on per week and (B) weekly distance traveled (km) for the control (blue), cocaine (orange), and metabolite (red) treatment groups extracted from the Bayesian generalized linear models (GLMs). Point estimates denote posterior medians, while error bars denote 89% CIs. Colored distributions represent the posterior distributions. See also [Tables S2](#) and [S3](#).

Broad-scale space use and dispersal

As expected, fish from all treatment groups were detected at the highest numbers in the southern portion of the lake during the initial 2 weeks of the study, which was close to their release site ([Figure 3](#)). However, fish in both the cocaine and metabolite groups demonstrated a more northward shift in their distribution during weeks 3 and 4 of the study, while the control group largely remained closer to the release site ([Figure 3](#)). This trend was exaggerated in the final month of the 8-week study period (i.e., weeks 5–8), where the metabolite-treatment group was found in the greatest numbers in the central-northern portion of Lake Vättern, while control group fish were primarily located in the southern area of the lake closer to the initial release site ([Figure 3](#)).

The treatment differences seen in broad-scale space use were supported by an analysis of maximum dispersal distance (i.e., maximum in-water distance between fish position and initial release site) across the study period ([Table S4](#)). Indeed, while the maximum dispersal distance from the release site for each fish did not substantially change across the 8-week study period in the control-treatment group (estimated change in maximum dispersal distance in km [89% CI] = 0.03 [−5.21, 5.40]), this was not true for fish in the cocaine-treatment group, which were increasingly detected farther away from the release site over the course of the study (estimated change in maximum dispersal distance in km [89% CI] = 4.46 [−0.93, 9.76]), albeit with uncertainty in the effect. This trend was further exaggerated in fish belonging to the metabolite-treatment group, which demonstrated the greatest maximum dispersal distances (estimated change in maximum dispersal distance in km [89% CI] = 10.97 [3.97, 18.38]). For example, during the final 2 weeks of the study, fish in the metabolite-treatment group were detected up to ~12.3 km (89% CI: 1.9, 24.0 km) farther away from the release site than those in the control group ([Table S4](#)), suggesting that exposure to the metabolite increased dispersal distances.

Tissue concentrations of cocaine and benzoylecgonine

A concurrent laboratory experiment on a separate group of fish ($n = 63$) revealed that cocaine was readily taken up from the implants into the brains of cocaine-treatment fish (mean = 42.85 [± 4.87] ng g^{−1}; range = 6.52–102.07 ng g^{−1}; [Figure 4](#); [Table S5](#)). As expected, all brain samples of fish from the metabolite-treatment group were below the limit of quantification for cocaine. Benzoylecgonine was also detected in the brains of cocaine-treatment fish (mean = 1.30 [± 0.41] ng g^{−1}; range = 0.33–11.27 ng g^{−1}) but at much lower concentrations than the parent compound. Benzoylecgonine was detected in the brains of metabolite-treatment fish (mean = 33.74 [± 6.85] ng g^{−1}; range = 6.77–158.03 ng g^{−1}), and at much higher concentrations than those found in the cocaine treatment. Neither cocaine nor benzoylecgonine was detected in any of the samples from control fish.

Brain concentrations showed an initial peak immediately after implantation, likely reflecting rapid release of the compound from the oil-carrier matrix. A later secondary rise in tissue concentration ([Figure 4A](#)) could, in principle, reflect delayed release due to the compound's behavior within the oil carrier. Indeed, broadly similar effects have been observed for fluoxetine,³⁹ as well as clobazam and tramadol³¹ when administered using the same slow-release implants. However, we note that a technical issue with the freezer in which the tissue samples for the laboratory component of the study were stored prior to analysis resulted in a freeze-thaw cycle that may have affected compound stability and recovery. We therefore advise caution when interpreting this secondary peak. More importantly, although brain concentration data for fish inhabiting cocaine-contaminated environments are scarce, the concentrations we measured fall within the likely range expected for organisms living in effluent-dominated systems. Indeed, treated wastewater effluent released into rivers has been shown to contain up to 2,990 ng L^{−1} of cocaine and 21,570 ng L^{−1} of benzoylecgonine,¹³ while a recent meta-analysis found maximum global surface water concentrations of 5,896 and 3,582 ng L^{−1} for cocaine and benzoylecgonine,

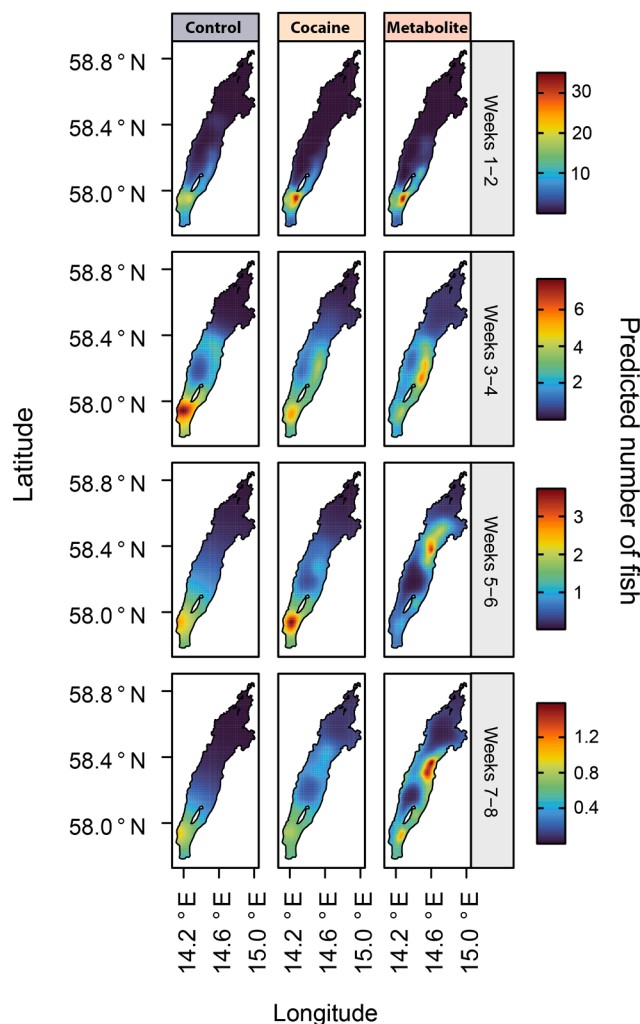


Figure 3. Spatial distribution of smolts across the study period
Estimated spatial distribution of Atlantic salmon smolts from the control-, cocaine-, and metabolite-treatment groups in Lake Vättern based on predictions for 800 × 800 m grid squares across the study area extracted from the generalized additive models for each study fortnight. Colored heatmaps represent the predicted number of individual fish detected per grid square, with the scale indicated on the right of each plot. Note: these plots are presented to interpret treatment differences in space use within each study fortnight. Care should be taken when making comparisons across study fortnights due to differences in the number of individual fish remaining in the lake over the study period.
See also Table S4.

respectively.¹⁴ Such concentrations exceed water concentrations predicted to result in cocaine hazards by fish plasma modeling.^{40,41} Further, prior analysis of wild sharpnose sharks found that muscle samples contained up to 107.5 ng g⁻¹ of cocaine and 18.7 ng g⁻¹ of benzoylecgonine,¹⁵ while previous analyses of cocaine in wild aquatic invertebrates reported maximum tissue concentrations of 67.6 and 30.8 ng g⁻¹ in *Echinogammarus marinus* and *Gammarus pulex* sampled from UK waterways, respectively.^{42,43} However, we acknowledge that comparisons across species and tissue types should be interpreted cautiously. Nevertheless, while systematic environmental

monitoring is limited, the brain cocaine (42.85 ± 4.87 ng g⁻¹) and benzoylecgonine (33.74 ± 6.85 ng g⁻¹) concentrations achieved in our experimental treatments are broadly consistent with exposures to fish residing in municipal effluent-dominated aquatic systems in regions where cocaine use is pronounced.

DISCUSSION

Illicit drug pollution is a rapidly emerging threat to aquatic ecosystems. However, we still know very little about how these potent neuroactive substances can affect the behavior and movement of non-target species in the wild. Here, in a large field-based experiment, we demonstrate that environmentally relevant levels of the common illicit pollutant cocaine and its main metabolite, benzoylecgonine, can accumulate in the brains of exposed fish and affect their movement and space use in the wild.

In line with predictions and previous laboratory studies,^{7,21,22} cocaine and benzoylecgonine increased the movement of exposed salmon smolts in the wild. This effect was particularly pronounced during the final 2 weeks of the 8-week study period. In particular, there were few differences in movement rates among treatment groups at the start of the 8-week study period, with all fish demonstrating high movement rates for the first 2 weeks after their release into Lake Vättern. However, fish in the control group decreased their weekly distance traveled and became more resident over time. This was less true of fish exposed to the cocaine and metabolite (i.e., benzoylecgonine) treatments, which maintained higher activity rates. This effect was particularly pronounced in the metabolite-exposed fish, which were estimated to swim almost 14 km farther per week than control fish in the final 2 weeks of the study. These results are in line with previous laboratory-based research in a variety of species reporting that cocaine administration can alter locomotor activity.^{16,21,22,44,45} Why metabolite-exposed fish only demonstrated increased movement rates when compared with controls during the final month of the study, and not at the beginning of the tracking period, is unclear. However, prior research has shown that hatchery-reared fish often demonstrate higher initial movement after release when compared with wild conspecifics^{46,47} and that these high movement rates quickly decrease as fish become familiar with their new environment.⁴⁸ Thus, the delayed divergence in activity among the treatment groups in this study aligns with evidence that hatchery-reared fish typically exhibit high initial movement post-release that naturally declines over time, suggesting that pollutant effects only emerged after this initial high-activity phase.

We also found that cocaine pollution altered the space use and dispersal patterns of Atlantic salmon smolts. Large-scale analyses of space use suggested that metabolite-exposed fish likely used more northern areas of the lake during the final month of the tracking period, when compared with both control and cocaine-exposed fish. Indeed, during the final 2 weeks of the study, metabolite-exposed smolts were found, on average, up to 12.3 km farther away from the release site than control fish, suggesting that exposure to benzoylecgonine promoted increased dispersal distances. This is in line with our predictions and prior laboratory studies, which found that cocaine pollution can alter organismal movement traits.^{7,21,22} However, to the best of our knowledge, this is the first demonstration that environmental levels of a cocaine

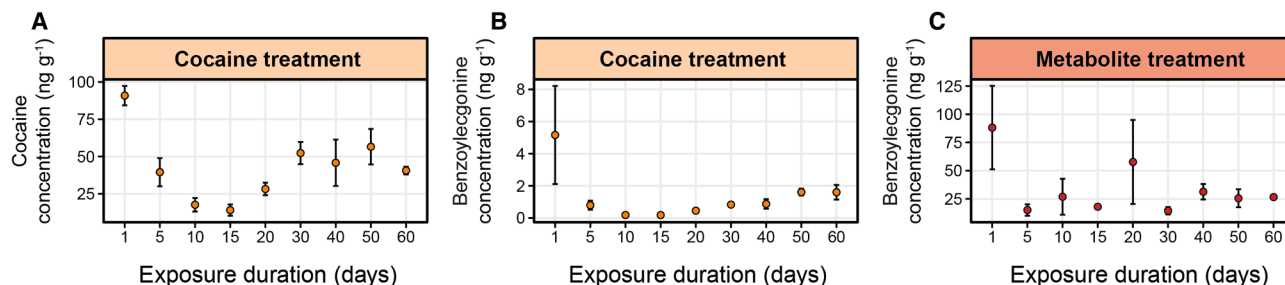


Figure 4. Levels of cocaine and benzoylecgonine in the brains of exposed fish

Brain concentrations (ng g⁻¹) of (A) cocaine and (B and C) benzoylecgonine in exposed fish over the course of 60 days. Point estimates represent means, while error bars denote ± 1 SE.

See also Table S5.

metabolite that is commonly found in aquatic ecosystems can alter the space use and swimming activity of fish in the wild. Although, we note that our measures of space use and locomotor activity were fairly coarse, only capturing relatively large-scale changes in fish behavior. Further, while our large telemetry array could detect fish across most of the lake, there were areas where fish could have been outside the detection range of the receivers. Future research using high-resolution acoustic telemetry that also incorporates fish depth use^{49–51} as well as newly developed predation tags⁵² will be needed to better identify how cocaine pollution affects the fine-scale spatial and movement dynamics of exposed fish and whether this influences survival.

Interestingly, we found that the metabolite (i.e., benzoylecgonine) treatment had a larger effect on smolt movement when compared with cocaine-treated fish. In humans, cocaine is primarily metabolized to benzoylecgonine, which typically has a longer half-life than cocaine and is often found at higher concentrations in blood samples than its parent compound.^{53,54} By contrast, benzoylecgonine was only detected at very low concentrations in the brains of fish exposed to cocaine in this study. Further, brain benzoylecgonine concentrations were much lower in the cocaine treatment compared with the metabolite treatment. While benzoylecgonine is often considered largely inactive in humans,⁵⁵ previous research has demonstrated that benzoylecgonine can be a more potent vasoconstrictor than cocaine.^{56,57} Specifically, benzoylecgonine was more potent in mammals than cocaine in eliciting vasoconstriction of fetal cerebral arteries, which, if this alpha-adrenergic stimulation mechanism extends to fish, could provide a potential mechanistic explanation for altered behavior and subsequently present longer-term bioenergetic consequences.⁵⁷ Moreover, prior work in fish has found that benzoylecgonine can have more pronounced effects on oxidative stress and energy metabolism than cocaine.⁵⁸ For example, after 14 days of exposure to 10 ng L⁻¹ of either cocaine or benzoylecgonine, zebrafish (*Danio rerio*) exposed to the metabolite exhibited greater oxidative stress in the brain when compared with fish exposed to the same concentration of cocaine⁵⁹ (however, this was exposure duration and dosage specific). Further, exposure to environmental levels of benzoylecgonine was found to alter the expression of proteins involved in energy metabolism and oxidative stress in zebrafish embryos—a result that was not seen after exposure to the same concentrations of cocaine.⁶⁰ Importantly, previous research has broadly linked energy metabolism and oxidative

status to animal behavioral and life-history traits,^{61–65} including in fish.⁶⁶ Whether the effects of benzoylecgonine exposure on salmon smolt movement and space use in this study were mediated by changes to energetic traits and oxidative status is not clear and will require future research. Nevertheless, our results suggest that the cocaine metabolite benzoylecgonine may pose an even greater risk in terms of disruptions to fish movement and behavior than its parent compound. This is particularly concerning because the potential cross-species hazards of environmental contaminants—such as pharmaceuticals and drugs of abuse—are often assessed based on the parent compounds rather than their metabolites,^{67,68} even though metabolites frequently occur at higher concentrations in surface waters. For example, benzoylecgonine is routinely detected at higher levels than cocaine itself in aquatic ecosystems.¹⁴

In summary, our findings demonstrate that environmentally relevant concentrations of cocaine and its major metabolite benzoylecgonine can accumulate in the brains of exposed Atlantic salmon—an ecologically and economically important species of high conservation concern²⁹—and disrupt the movement and space use of these fish in the wild. We also note that previous research has reported behavioral differences between wild and hatchery-reared Atlantic salmon,^{69,70} and determining whether the effects observed here are also present in wild fish will be important for future research. Additional key goals for research will be to determine the underlying mechanisms for these behavioral perturbations in fish, understand how widespread these effects are in the wild, identify areas most at risk from illicit drug pollution,⁷¹ and determine whether such observed alterations of movement and space use have long-term effects on fish reproduction and survival. Given the influence of animal movement on organismal fitness and population dynamics,^{72,73} these findings suggest that cocaine pollution may be added to the growing list of stressors affecting fish in the wild, with yet unknown consequences for long-term population persistence. These results highlight the importance of accounting for illicit drug pollutants when managing and conserving vulnerable aquatic species.

RESOURCE AVAILABILITY

Lead contact

Requests for further information and resources should be directed to and will be fulfilled by the lead contact, Jack A. Brand (jack.brand@slu.se).

Materials availability

This study did not generate any new, unique reagents.

Data and code availability

- All acoustic telemetry data and pharmaceutical data of water samples taken from Lake Vättern are publicly available on the open science framework online repository at [10.17605/OSF.IO/ZWBG7](https://doi.org/10.17605/OSF.IO/ZWBG7).
- All statistical code used to produce the results reported in this manuscript is publicly available on the open science framework online repository at [10.17605/OSF.IO/ZWBG7](https://doi.org/10.17605/OSF.IO/ZWBG7).

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AUTHOR CONTRIBUTIONS

M.G.B., D.P., D.C., E.S.M., G.H., and T.B. conceived the experiments. J.A.B., M.G.B., D.P., D.C., M.M., A.P.H.B., E.S.M., and G.H. conducted the experiments. J.A.B., M.G.B., D.P., D.C., E.S.M., G.H., J.F., and T.B. provided infrastructure, materials, and financial resources. J.A.B. analyzed the data and led the writing of the manuscript. All authors contributed to revising the final manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.

STAR★METHODS

Detailed methods are provided in the online version of this paper and include the following:

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SUPPLEMENTAL INFORMATION

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STAR★METHODS

KEY RESOURCES TABLE

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Chemicals, peptides, and recombinant proteins		
Cocaine hydrochloride	LGC GmbH	CAS: 53-21-4
Benzoylcegonine tetrahydrate	Sigma Aldrich	CAS: 5928-96-1
Deposited data		
Acoustic telemetry detection data	This study	10.17605/OSF.IO/ZWBG7
Pharmaceutical concentrations in water samples taken from Lake Vättern	This study	10.17605/OSF.IO/ZWBG7
Statistical code	This study	10.17605/OSF.IO/ZWBG7
Software and algorithms		
R	R Development Core Team ⁷⁴	https://www.r-project.org/

EXPERIMENTAL MODEL AND STUDY PARTICIPANT DETAILS

The study used acoustic telemetry detection data taken from two-year-old, hatchery-reared Atlantic salmon (*Salmo salar*) smolts in Lake Vättern, Sweden. All experimental procedures were approved by the Swedish Board of Agriculture (permit numbers: Dnr A.18.15 and Dnr 5.8.18).

METHOD DETAILS

Study site

The study was conducted in Lake Vättern, located in southern Sweden (Figure 1A). Lake Vättern is the second largest (surface area $\approx 1,912 \text{ km}^2$; maximum depth = 128 m; water volume $\approx 77 \text{ km}^3$) lake in Sweden. Due to its depth, the lake contains natural populations of cold-water species such as Arctic char (*Salvelinus alpinus*), in addition to populations of brown trout (*Salmo trutta*), whitefish (*Coregonus* sp.), grayling (*Thymallus thymallus*), and northern pike (*Esox lucius*).⁷⁵ Atlantic salmon (landlocked population) are also regularly stocked in the lake to support a recreational salmon fishery. Mean daily surface water temperatures in the lake (taken near the release site at Jönköping) ranged from $3.98 \pm 0.21 \text{ }^\circ\text{C}$ [mean $\pm$ SE] during the first 2 weeks of the study period to $7.60 \pm 0.16 \text{ }^\circ\text{C}$ during the final 2 weeks of the study period (Figure S1).

Slow-release implants

Fish were exposed to either cocaine or benzoylcegonine using previously validated slow-release chemical implants.^{34,36} These implants contain a known concentration of a target chemical suspended in a fat-based carrier, allowing the sustained exposure of fish to environmental levels of a contaminant of interest in the field. All implants in the current study were prepared using previously established protocols that have been reported elsewhere.^{31,35} Briefly, implants were prepared by dissolving either cocaine hydrochloride (CAS: 53-21-4, LGC GmbH, Luckenwalde, Germany) or benzoylcegonine tetrahydrate (CAS: 5928-96-1, Sigma Aldrich, Steinheim, Germany) in liquefied coconut oil (Kung's Markatta Virgin Coconut Oil) to reach a desired concentration of $50 \text{ } \mu\text{g}$ of drug per gram of implant. The solution was continuously stirred for 10 min to ensure sufficient mixing, before being sonicated in an ultrasound bath for a further 15 min at $30 \text{ }^\circ\text{C}$.³⁴ Control implants (i.e., coconut oil without cocaine or benzoylcegonine) were prepared following the exact same procedure, with the exception that neither cocaine nor benzoylcegonine were included. After preparation, implants were stored at $4 \text{ }^\circ\text{C}$ for 2 days prior to use. Before implantation, vials were gently warmed to $30 \text{ }^\circ\text{C}$ until the coconut oil was fully liquefied. Implants were maintained at $\sim 30 \text{ }^\circ\text{C}$ on a heated magnetic stirrer during tagging to ensure homogeneity, with temperature monitored continuously to avoid overheating. The mixture remained visually uniform throughout handling, and no phase separation or precipitation was observed before administration.

Experimental fish exposure and release

Two-year-old, hatchery-reared Atlantic salmon smolts ($n = 105$; body mass [mean $\pm$ SE] = 110 ± 2.5 g) were haphazardly selected from Klarälven landlocked stock held at the Gammelkroppa salmon hatchery ($59^\circ 41' 5.5''$ N, $14^\circ 18' 30.7''$ E) in 2022. While previous research has reported behavioral differences between wild and hatchery-reared Atlantic salmon,^{69,70} using hatchery fish provides critical experimental control in that it ensures that fish had not been previously exposed to contrasting developmental environments, and it allows us to standardize fish age and body size. This minimizes the chance that any treatment differences in movement are attributable to any potential confounding factors. All tagging and exposure methods followed previously published methods in juvenile salmonids.^{31,35} Briefly, approximately 3 to 4 days prior to release into Lake Vättern, all fish were anaesthetized in a tricaine methanesulfonate solution (MS-222; 0.15 g L^{-1} ; Sigma Aldrich, Steinheim, Germany), weighed, and measured (total length), before a small incision (~ 20 mm) was made into the abdomen on the ventral surface of the fish. The gills of each fish were kept constantly submerged in clean water throughout the minor procedure. Fish were implanted with an Innovasea V9 69 kHz acoustic tag (weight in air = 3.6 g; dB = 146; Innovasea Systems Inc., Bedford, NS, Canada) with an estimated maximum transmitter lifespan of 383 days, as well as a passive integrated transponder (PIT) tag (APT 12 mm tags; Biomark, Idaho, USA) that allowed for the identification of individual fish throughout the release. Acoustic tag implantation resulted in a tag burden (tag mass relative to body mass) of $\sim 3.5\%$ ($SD \pm 0.8\%$), which is within the recommended upper tag burden limits of 2–10%.⁷⁶ At the same time that each fish was tagged, they were given the slow-release implant so that fish were not anesthetized twice. Seventy haphazardly selected fish were administered an implant containing either cocaine ($n = 35$) or benzoylecgonine ($n = 35$) using a blunted 18-gauge needle at a dose of $5 \mu\text{L}$ of implant per gram of body mass (measured volumetrically in a syringe) in the same incision used for the transmitter insertion, in line with established protocols.³⁴ Using these methods, an average-sized fish (i.e., 110 g) would have received $\sim 550 \mu\text{L}$ of implant solution, delivering approximately $27.5 \mu\text{g}$ of drug to the fish. The remaining 35 fish received a control implant (i.e., an implant that did not contain a drug) using the same protocols. Together, this resulted in three treatment groups: cocaine ($50 \mu\text{g g}^{-1}$ of cocaine implant, as well as an acoustic tag and PIT tag), benzoylecgonine ($50 \mu\text{g g}^{-1}$ of benzoylecgonine implant, as well as an acoustic tag and PIT tag), and control (i.e., coconut oil implant without a drug, as well as an acoustic tag and PIT tag). The incision was then closed using two, non-absorbable silk sutures (Ethicon EH7149G). Following the procedure, fish were returned to holding tanks, where they were allowed to recover for 3 to 4 days prior to their release. All holding tanks were physically separated (i.e., no water exchange between tanks) and each was supplied with a constant stream of freshwater from a common water source at the same flow rate.

On April 12, 2022, all fish were released simultaneously into the south-western region of Lake Vättern ($57^\circ 56' 29.47''$ N, $14^\circ 7' 35.87''$ E). No mortality was recorded during transport from the hatchery to the lake, nor during release. An additional 200 untagged smolts were released alongside the experimental fish to reduce potential immediate predation pressure on experimental fish at the release site.

Fish tracking

Seventy-one acoustic receivers (VR2W, VR2AR, and VR2Tx, Innovasea Systems Inc., Bedford, NS, Canada) were deployed throughout Lake Vättern (Figure 1A) to track smolts equipped with acoustic transmitters (see Table S1 for exact receiver coordinates). As in previous studies,³⁵ receivers were attached to submerged buoys extending 3 m above the receiver to ensure that they were maintained in a vertical position in the water column. The weighted anchor on the bottom of the lake was separated from the receiver by a ~ 3 –5 m rope.

Chemical analysis of water samples

Surface water samples (150 mL ; $n = 4$) were collected from Lake Vättern, within a 1 km radius of the release site, to characterize the profile of 73 unique pharmaceutical and illicit drug pollutants in the area (see DataS1)—considering that dilute levels of these substances are present in nearly all human-impacted environments,^{77,78} and our previous research has documented effects of pharmaceutical pollution on salmonid movement dynamics in the wild.^{31,35} After collection, water samples were immediately kept at -20°C until extraction and subsequent analysis (see Preparation of samples and instrumental analysis). The analysis found that the study site was generally free from pharmaceutical pollution, apart from one sample where both diclofenac (anti-inflammatory, 7.8 ng L^{-1}) and finasteride (hormone inhibitor, 2 ng L^{-1}) were detected at low concentrations, and a separate sample where tramadol (opioid analgesic, 1 ng L^{-1}) was detected (see DataS1 for full water analysis results). Similarly, caffeine was detected in every sample (range = 102.2 – 226.1 ng L^{-1}), as well as in tap water (10.8 ng L^{-1}). Further, cocaine was detected in all water samples (range = 0.11 – 0.85 ng L^{-1}), while benzoylecgonine was detected in two samples (range = 0.07 – 1.05 ng L^{-1}), albeit both were detected at trace concentrations that are unlikely to achieve therapeutically active plasma levels and thus elicit biological effects. Moreover, cocaine (but not benzoylecgonine) was also detected at trace levels in tap water (0.56 ng L^{-1}) that was used as a processing blank during the sample extraction and analysis. While similar results have also been found in analyses of tap water from other European countries,⁷⁹ we advise caution in interpreting the cocaine and benzoylecgonine water analysis results as we cannot exclude the potential that concentrations of cocaine found in the water samples taken from the lake could be a result of contamination during the sample preparation and analysis in the laboratory.

Confirmation of chemical uptake in fish

As in previous research,^{31,35} we performed a laboratory experiment alongside our field study to confirm the uptake and accumulation of cocaine and benzoylecgonine in the tissues of Atlantic salmon smolts. Sixty-three, two-year-old Atlantic salmon smolts (body mass [mean $\pm$ SE] = 90.1 ± 3.1 g) were haphazardly collected from the Klarälven landlocked stock at the Gammelkroppa salmon hatchery and implanted with either a cocaine implant ($n = 27$), a benzoylecgonine implant ($n = 27$), or a control implant ($n = 9$), using

the exact same methods as employed in the field study (but without any acoustic tag). Fish were housed under standard hatchery conditions in tanks that were constantly supplied with fresh river water. Starting one day after implanting, three fish from both drug treatment groups were humanely euthanized in an MS-222 solution (0.3 g L^{-1}) and immediately frozen at -20°C for later chemical analysis, following previously reported methods.³⁵ This process was repeated for eight additional time points (i.e., 5 days, 10 days, 15 days, 20 days, 30 days, 40 days, 50 days, and 60 days) post-implantation. To maintain fish health and condition, salt (NaCl) was added to all fish tanks after 15 days post implantation, in line with standard hatchery practices. Similarly, starting ~ 28 days post-implantation, all fish were administered a short (90 min) Formalin solution (200 mg L^{-1}) bath every second day to help in managing potential parasites, in line with standard hatchery practices. In February 2025, brain tissue samples (sample mass [mean $\pm$ SE] = $95.3 \pm 1.7 \text{ mg}$) were extracted from each fish to identify the accumulation of cocaine and benzoylecgonine in exposed fish. Three control fish were each sampled at 1, 30, and 60 days post-implantation. Chemical analysis confirmed that no cocaine and/or benzoylecgonine were detected in the brains of control fish (i.e., all samples $<$ limit of quantification).

Preparation of samples and instrumental analysis

Water and tissue samples were prepared and analyzed based on established protocols described in earlier studies (see Table S6 for full list of pharmaceuticals and illicit substances screened).^{31,35} Briefly, water samples were prepared using solid-phase extraction: cartridges were conditioned with methanol, samples were spiked with isotopically labelled internal standards, passed through the cartridges, and the eluates were evaporated and reconstituted in methanol before analysis. Tissue samples were processed by repeated solvent extraction with acidified acetonitrile, after which the combined supernatants were evaporated and reconstituted in methanol. All analyses were performed using liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS). Specifically, a TSQ Quantiva triple quadrupole mass spectrometer (Thermo Scientific, San Jose, CA) fitted with a heated electrospray ionization (HESI) source was used to analyze both water samples and tissue extracts. To ensure analytical reliability, quality assurance and quality control (QA/QC) procedures included assessments of method precision, limit of quantification (LOQ), and the measurement of blank samples. Target compounds were quantified using the internal standard method. Instrumental LOQs were determined using a eight-point calibration curve, where the LOQ corresponded to the lowest calibration point achieving a signal-to-noise ratio of at least 10. The instrumental LOQ peak area for each target compound was used to calculate individual LOQs for each analyzed sample (see Table S6). Analytical precision was evaluated as the relative standard deviation (RSD) of response factors across the calibration range. Tissue sample concentrations falling below the LOQ were assigned a value equal to half the LOQ for statistical analyses, consistent with previously published practices³⁴ (Table S5).

QUANTIFICATION AND STATISTICAL ANALYSIS

All data analysis was performed in R (v. 4.2.2).⁷⁴ All analytical procedures followed those described in earlier studies.^{31,35} Briefly, we carried out initial data filtering to eliminate potential false detections using the *ATfitter*⁸⁰ and *tidyverse*⁸¹ packages. Following established methods,⁸² we excluded detections from individual fish that were observed only once within a 1-h window at a specific receiver, to reduce the potential for false detections. Abacus plots were examined for each fish to assess detection patterns. If an individual showed a prolonged period of consistent, frequent, and unchanging detections at a single receiver—suggesting no movement over weeks or months—we inferred that the fish had likely died and removed these data from further analyses. This was done blind to experimental treatment.

We employed Bayesian (generalized) linear models for all analysis using the *brms* package.⁸³ Post-hoc comparisons between treatment groups were executed using the *emmeans*⁸⁴ package and the *modelbased* package from the *easystats* suite.⁸⁵ All models were run for 2000–3000 iterations with 1000 warmup iterations, across four chains, and with weakly informative priors, as suggested by Lemoine.⁸⁶ To assess model adequacy, we performed posterior predictive checks and evaluated trace plots alongside the Gelman-Rubin diagnostic (all $\hat{R} = 1.00$). We report posterior medians along with 89% credible intervals (CIs) for all parameter estimates, following prior recommendations suggesting that these intervals offer greater reliability than 95% CIs when effective sample sizes are limited.^{87,88} When included as covariates, body mass (measured prior to initial release) and body condition (Fulton's K index⁸⁹) were mean-centered and scaled (mean = 0; SD = 1), enabling interpretation of effects relative to an average-sized fish in average condition (upon release). Similarly, study fortnight was left-centered and rescaled to vary between 0 and 1 when included as a covariate to facilitate model fitting (see Table S7 for a summary of model structures).

Apparent survival time

We began by assessing whether apparent survival time within the receiver array differed between exposure treatments. Following established approaches,³⁷ we estimated apparent survival time as the number of days between the tagging date of each individual fish and the corresponding final detection in the array. This approach may overestimate mortality, as it does not account for the possibility that some individuals may have survived but exited the array. However, due to the comprehensive coverage of the array and the landlocked nature of the Atlantic salmon population in this system, such cases are likely rare. Nevertheless, we refer to this measure as 'apparent survival time'.³⁸ Twelve smolts were right censored prior to analysis because their final detection either occurred on or after the expected end of their tag's battery life (based on tagging date plus estimated battery duration), or within five days of the study's conclusion. The five-day threshold was used because over 99% of movements between receivers occurred within this time-frame. To evaluate differences in apparent survival time between treatment groups (control, cocaine, or metabolite-exposed fish), we

fit a Bayesian generalized linear model assuming an exponential distribution. The duration of detection for each individual was used as the response variable, with censoring handled using the *cens()* function. Treatment was included as a fixed-effect predictor, while body mass (g) and body condition (Fulton's K) were added as scaled continuous covariates (mean = 0, SD = 1). We included body condition because prior studies have shown that it can influence survival in juvenile salmonids.⁹⁰

Movement dynamics

We restricted analyses of smolt movement and space use to the first 8 weeks (i.e., 56 days) of tracking, as this is when at least ~50% of fish in each treatment group were presumed to be alive and when we could be sure that exposed smolts had detectable levels of cocaine and benzoylecgonine present in their brain tissue (see Figure 4). We calculated the total number of unique receivers visited by each individual per week during the initial 8 weeks of tracking. The number of unique receivers visited by each fish per week was included as a response variable in a Bayesian generalized linear mixed-effects model with a Poisson distribution (log link). Treatment was included as a fixed-effect factor, while study fortnight (scaled), body mass (scaled), and body condition (scaled) were included as continuous covariates. We also included an interaction between treatment and study fortnight to investigate whether the treatment groups altered movement rates over the course of the study. Fish ID was also included as a random intercept to account for repeated measures.

To estimate the in-water distance travelled by each fish within the lake, we used a shapefile of the study area to construct a transition matrix and applied the *shortestPath()* function from the *gdistance* package.⁹¹ Due to overlapping detection ranges among some nearby receivers, we calculated 60-min centers of activity (COA) by averaging the longitude and latitude of detections for each fish.⁴⁹ This approach helped reduce the likelihood of inferring unrealistic movement patterns, such as rapid transitions between adjacent receivers. Predicted maximum swimming speeds were derived for each individual using body length measurements and the critical swimming speed formula for freshwater fish provided by Wolter and Arlinghaus.⁹² We excluded distances between consecutive COAs when the calculated swimming speed exceeded the predicted maximum speed for that individual smolt. The total in-water distance swam (in km) per week was then included as a response variable in a generalized linear mixed model. Due to the presence of zeroes in the data, we used a hurdle gamma distribution (log link). This model contained the same fixed- and random-effects structure as the model described directly above. In addition, we also included an interaction between treatment and study fortnight in the hurdle probability component of the model to account for treatment differences in the probability of moving (or not) across the study period.

Broad-scale space use and dispersal

Finally, we quantified differences in broad-scale space use and dispersal within the lake between the three treatment groups. Similar to Fall et al.,⁹³ we implemented a generalized additive model (GAM) using the *mgcv* package⁹⁴ to investigate variation in space use among the treatment groups. We used the *soapcheckr* package⁹⁵ to apply a soap film smoother in all GAMs in order to incorporate lake boundaries and local geographic features into estimates of smolt distributions.⁹³ For each study fortnight, the number of fish from each treatment group detected on a given receiver was included as a response variable in each model. We assigned values of zero to receivers present in the lake that registered no detections for a given study fortnight. Due to the presence of excess zeros, all models were fit with a zero-inflated Poisson distribution. Four separate models were constructed for each study fortnight. In all models, treatment was included as a fixed effect, while receiver location (bivariate spatial variable of longitude and latitude, in UTM coordinates) and distance from release site (scaled) were included as smooth functions. We calculated the smooths separately for each treatment group using the *by* function. To avoid overfitting, we restricted the number of base functions to 10 for distance from the release site, and 30 for receiver location. We accounted for any potential treatment differences in survival per study fortnight by including an offset function of the (logged) maximum number of individual fish recorded per treatment group within the study fortnight. Model performance was checked using the *appraise()* function from the *gratia* package,⁹⁶ while residuals were simulated using the *DHARMA* package.⁹⁷ We note that despite trying different distributions and model structures/parameters, there were still several issues with model fitting and diagnostics. While these issues were mostly minor, caution should be taken when interpreting these models. Nevertheless, we believe that the models still offer interesting insights into broad-scale spatial patterns of exposed smolts. Model-predicted plots of the number of fish detected for each treatment group were generated for 800 × 800 m grid squares across the study area using the *augment()* function from the *broom.mixed* package.⁹⁸ Approximately 0.7% of the predicted values exceeded the known maximum number of fish tagged in the system (i.e., during the first two weeks of the study). Therefore, all values were re-scaled for each treatment group to be in the range of the recorded values (0–35).

To further investigate potential treatment differences in spatial distribution and dispersal, we calculated the maximum in-water distance of each fish's COA from the initial release site for each study fortnight, similar to previous studies⁹⁹ (Table S4). The maximum in-water distance (in km) that fish were detected from the release site (i.e., maximum dispersal distance) per study fortnight was included as a response variable in a generalized linear mixed model with a gamma distribution (log link). This model contained the same fixed- and random-effects structure as the locomotor activity model described above, with the exception that there was no hurdle component to the model.