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Short communication

Short communication: An alternative pathway for melatonin synthesis in the skin of European flounder (*Platichthys flesus*)

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ABSTRACT

The classic melatonin biosynthesis pathway (Mel; *N*-acetyl-5-methoxytryptamine) involves two consecutive enzymatic steps that are decisive in hormone production: conversion of serotonin (5-hydroxytryptamine; 5-HT) to *N*-acetylserotonin (NAS) and the methylation of the last compound to Mel. This pathway requires the activity of the enzymes: the first is of the category of *N*-acetyltransferases (AANAT, SNAT, or NAT) and the second is *N*-acetylserotonin *O*-methyltransferase (ASMT; also known as HIOMT). However, quite recently, new information has been provided on the possibility of an alternative Mel synthesis pathway; it would include a two-step action by these enzymes, but in reverse order, where ASMT (or ASMTL, the enzyme related to ASMT) methylates 5-HT to 5-methoxytryptamine (5-MT), and then the last compound is acetylated by an enzyme of the category of *N*-acetyltransferases to Mel. In our study on the activity of enzymes in the Mel biosynthesis pathway in flounder skin, we have found an increase in 5-MT level, as a result of the increase in 5-HT concentration, which is followed by a growing concentration of Mel. However, we have not found any increase in Mel concentration, despite an increase in NAS in the samples. Our data strongly suggest an alternative way of Mel production in flounder skin in which 5-HT is first methylated to 5-MT, which is then acetylated to Mel.

Modern studies on melatonin (Mel; *N*-acetyl-5methoxytryptamine) began as early as 1917 when McCord and Allen observed a powerful blanching effect of the substance of pineal origin on the skin of tadpoles (McCord and Allen, 1917); thus, the story of Mel began in the skin. Melatonin, which is a product of tryptophan metabolism, has then been found in almost all life forms, from primitive photosynthetic bacteria to vertebrates, and it has been detected in various tissues and organs of vertebrates, including the skin (Huether, 1993; Hardelannd, 1999; Slominski et al., 2002, 2005, 2008; Kim et al., 2024). Melatonin has generally been accepted to be synthesized directly from serotonin (5-hydroxytryptamine; 5-HT) in enzymatically regulated paces determined by the Axelrod group in 1960 (Axelrod and Weissbach, 1960; Weissbach et al., 1960). This classic Mel biosynthesis pathway involves two successive enzymatic steps that are decisive for the production of the hormone: the conversion of serotonin to *N*-acetylserotonin (NAS) by aralkylamine *N*-acetyltransferase (AANAT), or arylamine *N*-acetyltransferase (SNAT; serotonin *N*-acetyltransferase, selective for indoleethylamines, or NAT, not selective for indoles) and the methylation of *N*-acetylserotonin by *N*-acetylserotonin *O*-methyltransferase (ASMT), also known as hydroxyindole *O*-methyltransferase (HIOMT) to Mel. For the record, this route requires the activity of the enzymes: the first is of the category of *N*-acetyltransferases (AANAT, SNAT, or NAT) and the second is a type of *N*-acetylserotonin *O*-methyltransferases (ASMT, ASMTL). It is worth highlighting here that AANAT, SNAT and NAT belong to the GNAT (GCN5-related *N*-acetyltransferase) superfamily (Vetting et al., 2005; Huang et al., 2022) and catalyze indolamine acetylation at different rates, depending on substrate specificity and concentration (Falcón et al., 1996, 2011; Gaudet et al., 1993); methyltranferase ASMT also presents different substrate specificity in various organs and tissues (Morton, 1987; Morton and Forbes, 1989; Pévet et al., 1981). However, quite recently, new information has been provided on the possibility of an alternative Mel synthesis pathway; this pathway would include a two-step action by these enzymes, but in reverse order, where ASMT (or enzyme related to ASMT) methylates 5-HT to 5-methoxytryptamine (5-MT), and then the last compound is acetylated by an enzyme of the category of *N*-acetyltransferases (Tan et al., 2016; Back et al., 2016). This reverse pathway is described in plants in which both routes can act concurrently (Back et al., 2016), but to the authors' knowledge, it has never been reported in vertebrates.

In actual fact, in teleost fish, several genes encode AANAT and ASMT

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isozymes (Huang et al., 2022). Up to three *aanat* genes (*aanat1a*, *aanat1b*, and *aanat2*) are reported; *aanat1a* and *aanat1b* are expressed in the retina, the nervous system, and peripheral tissues (some fish express both, while others express either of the isoforms), but expression of *aanat2* appears exclusively in the pineal organ (Paulin et al., 2015; Saha et al., 2019). For example, in the eyeball and skin of three-spined stickleback (*Gasterosteus aculeatus*) both *aanat1a* and *snat* are expressed (Pomianowski et al., 2020, 2023), but in the skin of European flounder, neither *aanat* nor *snat* is reported, although *aanat1* is present in the eyeball (Pomianowski et al., 2023). Regarding the *asmt* genes, *asmt* and *asmt2* have been found in the three-spined stickleback eyeball, and *asmt2* has been found in the skin (Pomianowski et al., 2020, 2023). However, in European flounder, only *asmtl* expression has been detected in the skin, but in the eyeball, up to three genes, *asmtl*, *asmt* and *asmt2* have been reported (Pomianowski et al., 2023). To be precise, in teleosts, the *asmtl* gene is a product of fusion between the *maf* and *asmt* genes and has been transcribed in peripheral organs of several species, including skin (Zhang et al., 2017). Detectable levels of *asmtl* mRNA have been found in nine European flounder organs, including skin (Pomianowski et al., 2021). However, to date, the function of the *asmtl* gene is unknown and probably differs from that of *asmt* considering its peripheral distribution (Zhang et al., 2017; Pomianowski et al., 2021). The question arises whether the transcript variants correspond to various active forms of enzymes (isozymes and/or isoforms) involved in different metabolic pathways in different organs and tissues. It should be mentioned that although the function of the enzymes AANAT1 (a and b) mainly comprises Mel synthesis in the retina and peripheral tissues, their other functions are also possible: enzymes can catalyze production of *N*-acetyldopamine (NAD) in addition to *N*-acetylserotonin (NAS), where AANAT1a could be more involved in dopamine acetylation, while AANAT1b would prefer serotonin as substrate (Paulin et al., 2015). It is also known that ASMT, in addition to the methylation of *N*-acetylserotonin (NAS) to Mel, may participate in the catabolism of 5-HT and its derivatives, such as HIAA (5-hydroxyindoleacetic acid) and HTOL (5-hydroxytryptofol) (Morton, 1987; Morton and Forbes, 1989; Pévet et al., 1981). Our group has also reported the presence of various transcripts of genes that encode AANAT and ASMT in the three-spined stickleback and suggested the activity of AANAT and ASMT isozymes in other metabolic pathways in addition to the 'melatonin' pathway (Kulczykowska et al., 2017; Pomianowski et al., 2020). Therefore, it can also be expected that various enzymes (isozymes and/or isoforms) might be involved in various Mel synthesis pathways in fish skin; in flounder skin, ASMTL and NAT seem to be good candidates. *Why?*

In the current study, we address the idea of the presence of the second alternative Mel synthesis pathway in flounder skin, in which both ASMTL and NAT are involved. We present data on the activity of enzymes and refer them to the results of our previous study on the cutaneous stress response system in fish (Pomianowski et al., 2020, 2023).

We conducted our research on adult female European flounder (*Platichthys flesus*). The fish (n = 4, total weight 189.5–374.7 g and length 262–365 mm) were caught in the Gulf of Gdańsk (southern Baltic Sea) out of the breeding season and transported to the Institute of Oceanology PAS (Sopot, Poland). They were acclimatized in 70-L aerated aquaria with brackish water (7 ppt) at a temperature of 10 ± 2 °C and 12 L:12D photoperiod for two weeks and fed frozen *Mytilus* sp. mussels once a day at 13:00. The fish were decapitated and skin samples were taken at midnight under red light and stored at −70 °C until enzyme activity analyses. The sample collection was performed at night because we expected that Mel synthesis can be rhythmic with maximal activity during the night.

Fish skin samples, before NAT and ASMTL analyses, were weighed (40–80 mg) and homogenized (Bead Ruptor Elite, Omni International, USA) in 1 mL of 0.1 M phosphate buffer (pH 6.8) with 10 μL of 1.2 mM AcCoA (acetyl coenzyme A; Sigma, St. Louis, MO, USA) for NAT analyses and in 1 mL of 0.1 M phosphate buffer (pH 7.9) with 0.25 mM SAM (S-(5′-adenosyl)-L-methionine chloride; Cayman Chemicals, Ann Arbor, MI, USA) for ASMTL analyses. The homogenates were then centrifuged at 10,000*g*, at 4 °C for 10 min.

The NAT activity assay was carried out according to Pomianowski et al. (2020) with modifications. The enzyme assay was carried out in the presence of a 30 μL supernatant aliquot, 15 μL of 1.2 mM AcCoA and 45 μL of various concentrations of serotonin (5-HT; Sigma-Aldrich, St. Louis, MO, USA) or various concentrations of 5-methoxytryptamine (5-MT; Sigma-Aldrich, Switzerland) at 10 °C for 60 min. The final concentrations of AcCoA and 5-HT, or 5-MT in the reaction mixture were 0.33 mM and 0.17–11.35 mM, or 0.26–8.4 mM, respectively. The reaction was stopped by adding 15 μL of 6 N perchloric acid (Sigma-Aldrich, St. Louis, MO, USA) and the mixture was centrifuged (10,000 *g*, 4 °C, 10 min). The product of the enzymatic reaction, NAS or Mel, was measured using the HPLC method.

The ASMTL activity test was performed according to Pomianowski et al. (2023) with modifications. The enzyme reaction was carried out in the presence of a 30 μL supernatant aliquot, 7 μL of 2.5 mM SAM and 8.5 μL of varying concentrations of *N*-acetyl serotonin (NAS; Sigma-Aldrich, St. Louis, MO, USA) or different concentrations of 5-HT at 10 °C for 60 min. The final concentration of SAM and NAS, or 5-HT in the reaction mixture was 0.5 mM and 0.07–4.2 mM, or 0.08–5.18 mM, respectively. The reaction was stopped by adding 14.5 μL of 6 N perchloric acid, the mixture was centrifuged (10,000 *g*, 4 °C, 10 min). The product of the enzymatic reaction, Mel or 5-MT, was measured using the HPLC method.

HPLC analyses were performed using the Agilent 1200 Series Quaternary HPLC System with a fluorescence detector (Agilent Technologies, Germany) according to Pomianowski et al. (2020) with modifications. Chromatographic separation was achieved on a ZORBAX Eclipse Plus C18 (150 mm × 4.6 mm ID, 3.5 μm; Agilent, USA). A gradient elution was applied. The mobile phase consisted of solvent A (10 mM ammonium acetate; pH 5) and solvent B (methanol). A linear gradient was established at 10–60 % eluent B in 20 min, with a flow rate of 0.5 mL/min and a column temperature of 30 °C. Fluorescence detection was performed at 350 nm with excitation at 230 nm. Identification of NAS, 5-MT, and Mel was performed by comparing the retention time of the sample with the appropriate standards.

Fig. 1 presents two potential Mel synthesis pathways in flounder skin, which are taken into account in this work: the classic pathway (reactions a and b) that is not effective in Mel synthesis and a hypothetical pathway (reactions c and d) where ASMTL and NAT are involved and Mel is produced. This figure refers to enzyme activities found in flounder skin homogenates that are shown in Fig. 2 (A, B, C and D):

1. 5-HT + NAT → NAS (reaction a): NAT activity increased linearly with increasing 5-HT concentrations (in the range of tested concentrations up to 5.68 mM) (Fig. 2A);
2. NAS + ASMTL→Mel (reaction b): neither ASMTL activity nor Mel formation was detected in reaction with NAS as a substrate (in the range 0.07–4.20 mM) in the presence of 0.5 mM SAM (Fig. 2B);
3. 5-HT + ASMTL→5-MT (reaction c): ASMTL activity increased with increasing 5-HT concentrations to reach a plateau (Fig. 2C). Kinetic analysis, determined from the Lineweaver-Burk graph, gave K_m = 2.45 ± 0.23 mM and V_{max} = 63.04 ± 6.25 pmol/mg tissue/h (means ± SEM);
4. 5-MT + NAT → Mel (reaction d): NAT activity increased with increasing 5-MT concentration to reach a plateau (Fig. 2D). Kinetic analysis, determined from the Lineweaver-Burk graph, gave K_m = 4.25 ± 0.65 mM and V_{max} = 122.14 ± 15.25 pmol/mg tissue/h (means ±SEM).

In this work, it appears that 5-HT is acetylated to NAS, and 5-MT is acetylated to Mel, so some enzyme of the category of *N*-acetyltransferases must be active in reactions a and d (Fig. 2 A, D). Furthermore, an enzyme of the type of *N*-acetylserotonin *O*-methyltransferases

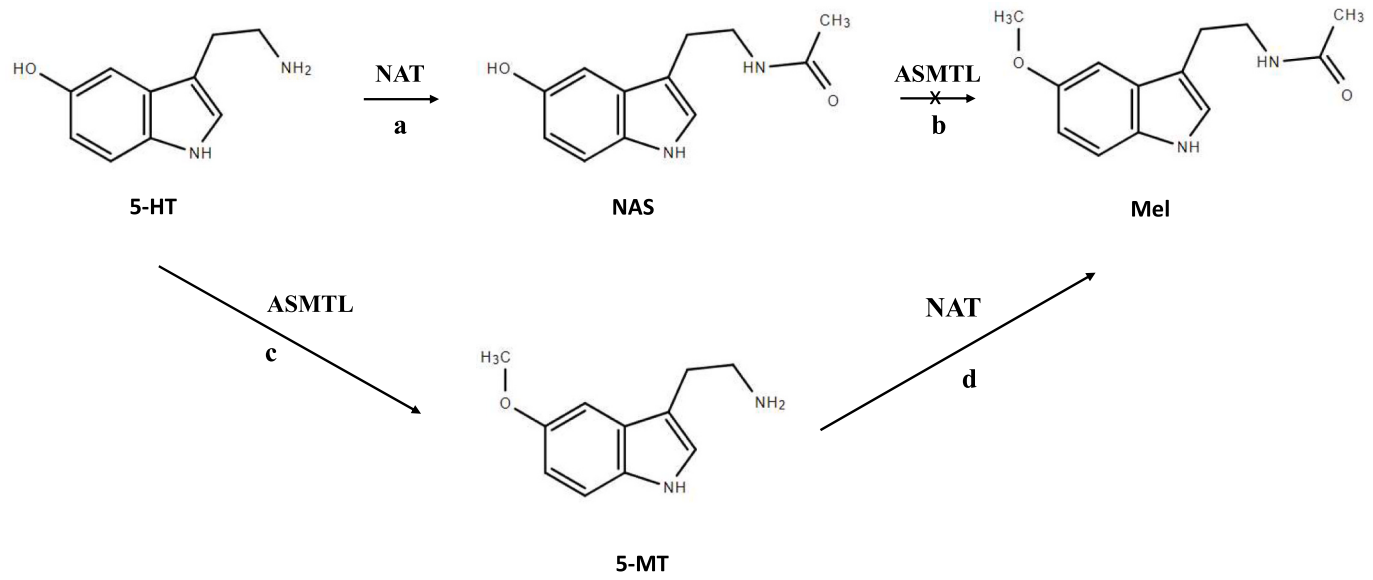

Fig. 1. Two hypothetical pathways to Mel synthesis in flounder skin. 5-HT, serotonin; NAS, *N*-acetylserotonin; Mel, melatonin; 5-MT, 5-methoxytryptamine; NAT, *N*-acetyltransferase; ASMTL, *N*-acetylserotonin *O*-methyltransferase like; a, 5-HT + NAT → NAS (reaction a); b, NAS + ASMTL→Mel (reaction b); c, 5-HT + ASMTL→5-MT (reaction c); d, 5-MT + NAT → Mel (reaction d);, no Mel formation.

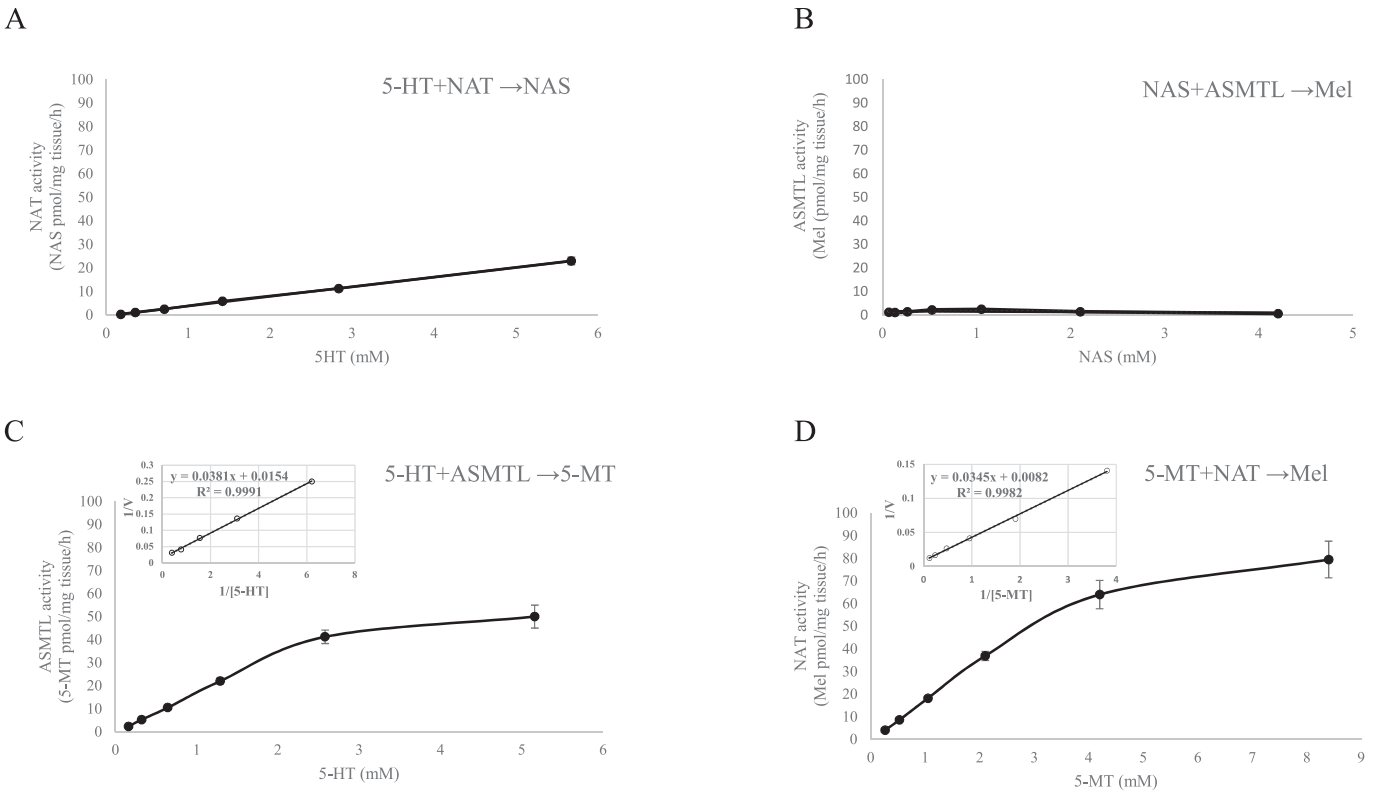

Fig. 2. NAT and ASMTL activities in flounder skin homogenates ($n = 4$; means ± SEM).
A (reaction a: 5-HT + NAT → NAS: NAT activity as a function of 5-HT concentration. Skin homogenates were incubated in the presence of AcCoA (acetyl coenzyme A; 0.33 mM);
B (reaction b: NAS + ASMTL→Mel: ASMTL activity as a function of NAS concentration. Skin homogenates were incubated in the presence of SAM (S-(5′-adenosyl)-L-methionine; 0.5 mM);
C (reaction c: 5-HT + ASMTL→5-MT): ASMTL activity as a function of 5-HT concentration. Skin supernatants were incubated in the presence of SAM (0.5 mM);
D (reaction d: 5-MT + NAT → Mel): NAT activity as a function of 5-MT concentration. The skin supernatants were incubated in the presence of AcCoA (0.33 mM).
All reactions were carried out at 10 oC for 60 min.
The insets correspond to 1/v (velocity) versus 1/[S] (substrate concentration).

methylates 5-HT to 5-MT (reaction c) but does not methylate NAS in reaction b (Fig. 2 B, C). Recalling our previous research in European flounder, no expression of *asmt* has been detected in the skin; instead, the expression of the *asmtl* gene has been found (Pomianowski et al., 2023). Although the role of ASMTL is still unknown, the presence of the catalytic domain of S-adenosyl-L-methionine binding in the C-terminal region argues for its methyltransferase activity (Tchigvintsev et al., 2013). Most probably, ASMTL has an affinity for 5-HT as a substrate. The lack of ASMTL activity with NAS as a substrate, resulting in the lack of Mel synthesis, excludes the possibility of the classic pathway of this indole production in flounder skin. Thus, an alternative way of Mel synthesis is strongly suggested: reactions c and d lead to Mel production. It seems that reactions a and d can be catalyzed by NAT, because neither the expression of *aanat* nor *snat* has been detected in the skin of flounder; unfortunately, the expression of *nat* has not been studied (Pomianowski et al., 2023).

In our previous study on the cutaneous stress response system in fish (Pomianowski et al., 2020, 2023), the lack of expression of any gene encoding AANAT or SNAT in flounder skin strongly suggested that Mel is not produced in the skin of this species, but is transported solely by circulation. However, we did not take into account the potential role of NAT, *N*-acetyltransferase, which is not selective for indoles. So far, the role of isozymic forms of NAT in the acetylation of serotonin has been described by Slominski et al. (2003) in mouse skin. They showed the ability to acetylate serotonin in the skin of C57BL/6 mice with genetic defects, namely 'knockdown' for AANAT (Slominski et al., 2003). Furthermore, Slominski's research group raised the possibility that both NAT and AANAT can participate in serotonin acetylation in mammalian skin (Slominski et al., 2005). Thus, also in flounder skin, NAT, instead of highly specific AANAT for indoles, could be involved in Mel synthesis, and consequently, Mel detected in the skin can be of local origin but not transported solely by circulation, as we previously stated. Furthermore, we then considered only the classic way of Mel synthesis, but now, in light of the new research concepts mentioned above and the results of our current study, we must take into account the possibility of an alternative Mel synthesis pathway in flounder skin that would include a two-step action by the enzymes, where ASMTL methylates 5-HT to 5-MT, which is then acetylated by NAT to Mel. However, in the future, it would be necessary to carry out the experiment during the day and at night and measure enzyme activity together with concentrations of 5-HT, 5-MT, and Mel in the sampled skin to provide more information on the relationship between the components of this metabolic pathway.

In this study, we demonstrate that ASMTL is active in the reaction that leads to 5-MT formation, where 5-HT is a substrate, but not in the reaction where NAS is a substrate. It agrees with Zhang et al. (2017) suggesting that the affinity of ASMTL for both substrates, 5-HT and NAS, may differ. Although Mel is not produced in the classic Mel synthesis pathway, NAS is still produced, so an activity of *N*-acetyltransferase (probably NAT) is required. This acetyltransferase has an apparent affinity for 5-MT. Because NAS is known as an active and efficient antioxidant and its protective effect against oxidative damage is independent of the effect of Mel (Wölfler et al., 1999; Oxenkrug, 2005; Galano and Reiter, 2018), its presence in the skin in high concentrations as a final product of 5-HT acetylation is physiologically justified. Furthermore, studies of human skin by Slominski et al. (2020) strongly recommend that NAS is a part of a local neuroendocrine system involved in the control of skin homeostasis (Slominski et al., 2020). Taken together, our data strongly suggest an alternative way of Mel production in flounder skin, where 5-HT is first methylated to 5-MT, which is then acetylated to Mel.

Ethics statement

All experiments complied with EC Directive 2010/63/EU for animal experiments and the guidelines and approval of the Ethics Committee for Animal Experimentation (University of Science and Technology, Bydgoszcz, Poland).

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CRediT authorship contribution statement

Magdalena Gozdowska: Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Joanna Stoń-Egiert:** Methodology. **Ewa Kulczykowska:** Writing – original draft, Supervision, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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