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Ocena znaczenia interocepcji u osób uzależnionych od alkoholu

Rozprawa na stopień naukowy doktora nauk medycznych i nauk o zdrowiu
w dyscyplinie nauki medyczne

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Motto

Nie mógł nawet wsłuchać się w bicie serca, jak robił to dawniej, chcąc wyciszyć wszystkie żale i udręki; nie miał już przecież serca.

Radek Rak, *Baśń o wężowym sercu albo wtóre słowo o Jakóbie Szeli*

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Spis treści

Wykaz stosowanych skrótów

BSI	Brief Symptom Inventory
EKG	elektrokardiogram
ICD-10	10th revision of the International Statistical Classification of Diseases and Related Health Problems
HCT	Heartbeat Counting Test
NE	negatywna emocjonalność
PSQ	Pain Sensitivity Questionnaire
SPA	substancje psychoaktywne
TAS-20	Toronto Alexithymia Scale
UA	uzależnienie od alkoholu
VAS	Visual Analogue Scale

Streszczenie

Ocena znaczenia interocepcji u osób uzależnionych od alkoholu

1. Wstęp

Interocepcja to zdolność organizmu do tworzenia ośrodkowych reprezentacji jego stanów wewnętrznych, która obejmuje procesy fizjologiczne odpowiedzialne za odbieranie, przetwarzanie i integrację ośrodkową sygnałów napływających z wnętrza ciała. Wyodrębnia się różne jej domeny, odnoszące się do oceny indywidualnych umiejętności identyfikowania sygnałów płynących z wnętrza ciała: [1] mierzoną behawioralnie **dokładność interoceptywną** (*interoceptive accuracy*), [2] mierzoną kwestionariuszowo **wrażliwość interoceptywną** (*interoceptive sensibility*) i [3] metapoznawczą **świadomość interoceptywną** (*interoceptive awareness*). Współczesne badania pokazują, że znaczenie interocepcji wykracza poza fizjologiczne mechanizmy homeostazy i jest istotne w procesach poznawczych, emocjonalnych czy regulacji zachowań. Zaburzenia interocepcji powiązano z przebiegiem wielu zaburzeń psychicznych, w tym uzależnień od substancji psychoaktywnych (SPA).

Dostępne w literaturze dane sugerują potencjalne wzajemne związki pomiędzy interocepcją a uzależnieniem od alkoholu (UA), przy czym uzasadnione wydaje się założenie, że zależność jest dwukierunkowa. Zaburzenie w zakresie prawidłowego odczytywania sygnałów napływających z ciała może sprzyjać rozwojowi UA. Alkohol może z kolei niekorzystnie wpływać na zdolności interoceptywne. Dodatkowo uwagę zwracają teoretyczne powiązania pomiędzy interocepcją a innymi, zidentyfikowanymi czynnikami ryzyka uzależnienia od alkoholu, takimi jak aleksytymia czy ból.

Aleksytymia, czyli trudność w nazywaniu własnych stanów emocjonalnych, występuje u 30-67% osób z rozpoznaniem UA. Niektóre teorie emocji zakładają, że prawidłowe odczytywanie sygnałów napływających z wnętrza ciała stanowi podstawę właściwego identyfikowania stanów emocjonalnych, co sugeruje związek aleksytymii z interocepcją. Co interesujące, aleksytymia określana bywa w literaturze jako „ogólny deficyt interocepcji".

Osoby uzależnione od alkoholu często zgłaszają występowanie przewlekłego bólu. Problem może dotyczyć ponad 30% z nich. Według niektórych konceptualizacji uzależnienie od alkoholu opisać można jako „przewlekłe zaburzenie bólowe". Ponadto ból wymieniany jest w literaturze przedmiotu wśród odczuć interoceptywnych.

Zarówno aleksytymia, jak i ból są związane z negatywną emocjonalnością (nieprzyjemne odczucia takie jak napięcie czy lęk), która może przyczyniać się do rozwoju UA. Znaczenie negatywnej emocjonalności w tym kontekście określają teorie negatywnego wzmacniania (zakładają one, że alkohol pomaga redukować nieprzyjemne stany emocjonalne).

Ocena zdolności interoceptywnych w populacji pacjentów uzależnionych od alkoholu wydaje się zatem ważnym kierunkiem badawczym i choć modele teoretyczne w przekonujący sposób wskazują na znaczenie tych zdolności w rozwoju i przebiegu UA, tak naprawdę niewiele jest badań w praktyce podejmujących tę tematykę. W szczególnym stopniu dotyczy to złożonych modeli uwzględniających związki interocepcji z innymi zmiennymi w grupie osób z UA, takimi jak: aleksytymia, ból i negatywna emocjonalność. Ponadto warto podkreślić, że dotychczas nie prowadzono badań, które porównywałyby wspomniane powyżej związki pomiędzy kliniczną grupą osób uzależnionych od alkoholu a grupą kontrolną osób zdrowych. Warto podkreślić, że analizy wspomnianych zależności mogą nieść istotne walory kliniczne, a uzyskane wyniki mogą potencjalnie znaleźć zastosowanie w ciągle niewystarczająco skutecznych programach terapeutycznych dla osób uzależnionych od alkoholu.

2. Cel pracy

Przedmiotem niniejszej pracy doktorskiej była ocena zależności pomiędzy dokładnością interoceptywną a aleksytymią, negatywną emocjonalnością (lękiem) i wrażliwością na ból u osób z rozpoznaniem UA.

Sformułowano następujące cele szczegółowe:

1. Porównanie dokładności interoceptywnej między grupą osób z rozpoznaniem UA a grupą osób zdrowych.
2. Ocena zależności między dokładnością interoceptywną, aleksytymią i negatywną emocjonalnością (lękiem) w grupie osób z rozpoznaniem UA.
3. Ocena związków między dokładnością interoceptywną i wrażliwością na ból w grupie osób z rozpoznaniem UA i grupie kontrolnej osób zdrowych.

3. Materiał i metody

W opracowaniu grupę badawczą stanowili pacjenci całodobowego oddziału terapeutycznego dla osób uzależnionych od alkoholu spełniający kryteria rozpoznania UA

zawarte w Międzynarodowej Klasyfikacji Chorób ICD-10: F10.2 (10th revision of the International Statistical Classification of Diseases and Related Health Problems). Grupa kontrolna składała się z osób, u których wykluczono rozpoznanie uzależnienia od alkoholu i innych zaburzeń psychicznych (zdrowi dorośli). Do badania zrekrutowano łącznie 165 pacjentów z rozpoznaniem UA i 110 zdrowych dorosłych. W celu oceny badanych zmiennych wykorzystano następujące kwestionariusze: [1] Skala Aleksytymii TAS-20 (*Toronto Alexithymia Scale* – najczęściej stosowanie narzędzie oceny nasilenia aleksytymii); [2] Krótki Inwentarz Objawów BSI (*Brief Symptom Inventory* – kwestionariusz służący do oceny objawów lękowych jako miary negatywnej emocjonalności); [3] Skala Wrażliwości na Ból PSQ (*Pain Sensitivity Questionnaire*); [4] Wzrokowo-Analogowa Skala Bólu VAS (*Visual Analogue Scale*); [5] Test Zliczania Uderzeń Serca HCT (*Heartbeat Counting Task* – test behawioralny służący do oceny dokładności interoceptywnej, który polega na zliczaniu uderzeń serca w wyznaczonych interwałach czasowych pod kontrolą EKG).

4. Wyniki

W wyniku przeprowadzonych analiz statystycznych stwierdzono, że osoby z UA cechowały się istotnie gorszą dokładnością interoceptywną i wyższą aleksytymią niż osoby zdrowe. W obu grupach gorsze zdolności interoceptywne były związane ze znamiennie wyższym nasileniem lęku. Wykazano dodatkowo ujemną korelację między dokładnością interoceptywną a aleksytymią w obu grupach – badani charakteryzujący się gorszym przetwarzaniem sygnałów napływających z wnętrza ciała mieli istotnie większe trudności w rozpoznawaniu swoich stanów emocjonalnych. W obu grupach wyższa aleksytymia była związana z większym nasileniem lęku, ale zależność ta okazała się istotna statystycznie tylko u osób z rozpoznaniem UA. W wyniku analizy modelu moderowanej mediacji stwierdzono, że aleksytymia pełniła rolę mediatora zależności pomiędzy dokładnością interoceptywną a negatywną emocjonalnością (lękiem). Efekt ten był istotnie większy w grupie osób z rozpoznaniem UA.

W analizach raportowanych w drugiej pracy oryginalnej stwierdzono, że badani z rozpoznaniem UA zgłaszali istotnie większe nasilenie bólu niż osoby zdrowe. W grupie klinicznej obserwowano również znamiennie większą wrażliwość na ból w porównaniu do grupy kontrolnej. W grupie osób uzależnionych od alkoholu mniejsze zdolności interoceptywne mierzone behawioralnie wiązały się z istotnie większą wrażliwością na ból. W grupie kontrolnej osób zdrowych nie obserwowano w tych analizach istotnych statystycznie związków,

uwidaczniał się jednak trend sugerujący odwrotną zależność (tj. lepsza dokładność interoceptywna wiązała się z większą wrażliwością na ból).

5. Wnioski

1. Osoby z rozpoznaniem UA charakteryzują się istotnie gorszą dokładnością interoceptywną niż osoby zdrowe.
2. (A) U osób z rozpoznaniem UA gorsza dokładność interoceptywna jest istotnie związana z wyższą aleksytymią i większą negatywną emocjonalnością (lękiem). (B) Aleksytymia jest mediatorem zależności między dokładnością interoceptywną a negatywną emocjonalnością (lękiem).
3. U osób z rozpoznaniem UA gorsza dokładność interoceptywna jest istotnie związana z większą wrażliwością na ból, podczas gdy u osób zdrowych obserwowana jest odwrotna zależność.

Summary

Significance of interoception in alcohol use disorder

1. Introduction

Interoception is the ability of an organism to create cortical representations of its internal states, which includes physiological processes responsible for receiving, processing and cortical integration of signals arising from within the body. Its various domains, referring to one's individual ability to properly identify internal states, were identified: [1] behaviorally measured **interoceptive accuracy**; [2] self-reported **interoceptive sensibility**, and [3] metacognitive **interoceptive awareness**. Current research shows that the importance of interoception extends beyond physiological mechanisms of homeostasis and is relevant to cognitive, emotional or behavioral regulatory processes. Interoceptive abnormalities have been recognized in many psychiatric disorders, including substance use disorders (SUD).

The current state of research suggests a potential interrelationship between interoception and alcohol use disorder (AUD), and it seems reasonable to assume that the relationship is bidirectional. A disturbance in the accurate perception of bodily signals may promote the development of AUD. Alcohol, in turn, may adversely affect interoceptive abilities. In addition, the theoretical links between interoception and identified AUD risk factors such as alexithymia and pain seem interesting.

Alexithymia, a difficulty in identifying one's own emotional states, is found in 30-67% of individuals with AUD. Some theories of emotion assume that the perception of signals coming from inside the body is the basis for the proper identification of emotional states, suggesting a link between alexithymia and interoception. Interestingly, alexithymia is sometimes referred to in the literature as a "general deficit of interoception."

Individuals with AUD often report chronic pain. The problem may affect more than 30% of them. According to some conceptualizations, alcohol addiction can be described as a "chronic pain disorder." Moreover, pain is considered one of the interoceptive phenomena.

Both alexithymia and pain are associated with negative affect (unpleasant feelings such as tension or anxiety), which can contribute to the development of AUD. The importance of negative affect in this context is determined by negative reinforcement theories (they assume that alcohol helps reduce unpleasant emotional states).

Therefore, the evaluation of interoceptive abilities in individuals with AUD seems to be an important research direction, and while theoretical models convincingly point to the importance of these abilities in the development and course of AUD, there are actually few studies addressing this issue. This is particularly relevant for complex models that take into account the relationship between interoception and other variables in AUD individuals such as alexithymia, pain and negative affect. In addition, it is noteworthy that there have been no studies to date comparing the aforementioned relationships between AUD individuals and healthy controls. Moreover, the analyses of these relationships may have significant clinical value, and the results may potentially be applied to the treatment programs for AUD individuals.

2. Objectives

The purpose of this dissertation was to assess the relationship between interoceptive accuracy and alexithymia, negative affect (anxiety) and pain sensitivity in individuals with a diagnosis of AUD.

The following specific aims were defined:

1. To compare interoceptive accuracy between individuals with AUD and healthy controls.
2. To evaluate the relationship between interoceptive accuracy, alexithymia, and negative affect in individuals with AUD.
3. To investigate the associations between interoceptive accuracy and pain sensitivity in individuals with AUD and healthy controls.

3. Material and methods

In this study, the experimental group consisted of patients of 24-hour therapeutic unit who met the criteria for the diagnosis of alcohol dependence provided by the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10): F10.2. The control group consisted of individuals in whom the diagnosis of AUD and other mental disorders was excluded (healthy adults). A total of 165 patients with a diagnosis of AUD and 110 healthy adults were recruited for the study. The following questionnaires were used to assess the study variables: [1] Toronto Alexithymia Scale TAS-20 (the most commonly used tool to assess the severity of alexithymia); [2] Brief Symptom Inventory BSI (a questionnaire

used to assess anxiety symptoms as a measure of negative affect); [3] Pain Sensitivity Questionnaire PSQ; [4] Visual Analogue Scale of Pain VAS; [5] Heartbeat Counting Task HCT (a behavioral test to assess interoceptive accuracy that involves counting heartbeats at designated intervals under ECG control).

4. Results

Statistical analyses showed that individuals with AUD had significantly worse interoceptive accuracy and higher alexithymia than healthy controls. In both groups, poorer interoceptive abilities were associated with significantly higher anxiety severity. In addition, there was a negative correlation between interoceptive accuracy and alexithymia in both groups – individuals characterized by poorer processing of bodily signals had significantly greater difficulty in recognizing their emotional states. In both groups, higher alexithymia was associated with higher anxiety severity, but the relationship proved statistically significant only in those with a AUD diagnosis. An analysis of the moderated mediation model found that alexithymia mediated the relationship between interoceptive accuracy and negative affect (anxiety). This effect was significantly greater in individuals with AUD.

In analyses reported in the second original paper, it was found that individuals with AUD reported significantly higher pain severity than healthy controls. The experimental group also showed significantly higher pain sensitivity compared to the control group. In individuals with AUD, lower interoceptive abilities measured behaviorally were associated with significantly greater pain sensitivity. In the control group of healthy adults, no statistically significant relationships were observed in these analyses, but a trend suggesting an inverse relationship (i.e., better interoceptive accuracy was associated with greater pain sensitivity) became apparent.

5. Conclusions

1. Individuals with a diagnosis of AUD have significantly worse interoceptive accuracy than healthy controls.
2. (A) Worse interoceptive accuracy is significantly associated with higher alexithymia and greater negative affect (anxiety) in individuals with AUD. (B) Alexithymia is a mediator of the relationship between interoceptive accuracy and negative affect (anxiety).

3. In individuals with AUD, worse interoceptive accuracy is significantly associated with greater sensitivity to pain, while the opposite relationship is observed in healthy controls.

Wstęp

Interocepcja, czyli proces analizy informacji napływających z wnętrza ciała, zyskuje coraz większe zainteresowanie naukowców. W efekcie zmienia się jej rozumienie. Na początku XX wieku Sherrington (1) po raz pierwszy użył określenia „interoceptywny" do opisania receptorów zlokalizowanych na narządach wewnętrznych, które odbierały sygnały czucia trzewnego (dla odróżnienia ich od receptorów eksteroceptywnych zaangażowanych w odbieranie informacji pochodzących ze środowiska zewnętrznego). We współczesnych definicjach interocepcja obejmuje ogół procesów fizjologicznych odpowiedzialnych za odbieranie, przetwarzanie i integrację sygnałów napływających z wnętrza ciała prowadzących do utworzenia ośrodkowej reprezentacji środowiska wewnętrznego (2, 3). Współcześnie wśród zjawisk interoceptywnych wymienia się na przykład głód i pragnienie, ale również odczuwanie temperatury czy bólu (3). Informacja na temat stanu wewnętrznego organizmu (sygnał interoceptywny) dociera do ośrodkowego układu nerwowego różnymi drogami. W największym stopniu proces ten zachodzi za pośrednictwem dróg wstępujących sympatycznej i parasympatycznej części autonomicznego układu nerwowego (3). Nie można jednak pominąć znaczenia dróg niezwiązanych z układem nerwowym, czego przykładem może być chociażby przekaźnictwo endokrynne. Przez wiele lat centralną rolę w przetwarzaniu sygnałów interoceptywnych na poziomie ośrodkowego układu nerwowego przypisywano korze wyspy (3). Ostatnie badania pokazują, że inne ośrodki korowe, takie jak kora przedniej części zakrętu obręczy czy kora oczodołowo-czołowa również pełnią w tym procesie ważną rolę (2). Według najnowszych konceptualizacji przekazywanie informacji pomiędzy wnętrzem ciała a ośrodkowym układem nerwowym przebiega dwukierunkowo, co pozwala nie tylko na monitorowanie, ale również regulowanie środowiska wewnętrznego (2). Co więcej, badania pokazują, że znaczenie interocepcji wykracza poza fizjologiczne mechanizmy homeostazy i jest istotne w procesach poznawczych, emocjonalnych czy regulacji zachowań (4). Teorie emocji przedstawione niezależnie przez James'a i Lange'a zakładały, że to fizjologiczne zmiany w ciele wyzwalają emocje (5). Współczesne teorie ucieleśnienia (*embodiment theories*) podkreślają znaczenie cielesnych stanów wewnętrznych dla procesów poznawczych czy emocjonalnych (4). Według tych teorii ciało wchodzące w bezpośrednie interakcje ze środowiskiem zewnętrznym pozwala na wytworzenie specjalnego dla danego doświadczenia wzoru aktywności w ośrodkach czuciowych i ruchowych. Wzór ten jest przechowywany w pamięci długotrwałej i aktywowany w podobnych okolicznościach, co pozwala na przykład rozpoznać poznany wcześniej obiekt lub odczuć doświadczoną w danym kontekście emocję.

W literaturze wyodrębnia się różne domeny interocepcji, odnoszące się do oceny indywidualnych umiejętności identyfikowania sygnałów płynących z wnętrza ciała. Najbardziej popularny model wyróżnia [1] mierzoną behawioralnie **dokładność interoceptywną** (*interoceptive accuracy, interoceptive sensitivity*); [2] mierzoną kwestionariuszowo **wrażliwość interoceptywną** (*interoceptive sensibility*) oraz [3] **świadomość interoceptywną** (*interoceptive awareness*) będącą metapoznawczą miarą oceny dokładności interoceptywnej (6). Najbardziej popularnym testem służącym do pomiaru dokładności interoceptywnej jest Test Zliczania Uderzeń Serca (*Heartbeat Counting Task, HCT*) (7), który uważany jest za pomiar obiektywny. Zadaniem badanego w tym teście jest ocena liczby uderzeń serca w wyznaczonych interwałach czasowych, którą następnie porównuje się z rzeczywistą liczbą uderzeń serca mierzoną za pomocą EKG. Istnieją również testy, które służą do badania interocepcji w innych wymiarach – na przykład oddechowym czy gastrycznym (8). Najczęściej wykorzystywanym kwestionariuszem do pomiaru wrażliwości interoceptywnej jest Wielowymiarowa Ocena Świadomości Interoceptywnej MAIA (*Multidimensional Assessment of Interoceptive Awareness*)[1] (9).

Zaburzenia interocepcji (a więc trudności w identyfikowaniu sygnałów płynących z wnętrza ciała) powiązano z przebiegiem wielu zaburzeń psychicznych, w tym uzależnień od substancji psychoaktywnych (SPA) (10). Użycie SPA powoduje zmiany w ciele (11). Na skutek przyjęcia SPA interoceptywne mechanizmy regulacyjne ulegają zaburzeniu, a homeostaza zostaje zachwiana. Powtarzające się używanie SPA prowadzi do utrwalenia się zmian w środowisku wewnętrznym (allostaza). W konsekwencji zmianie ulega ośrodkowa (głównie wyspowa) reprezentacja stanów wewnętrznych. Ustala się nowy „punkt odniesienia" dla mechanizmów regulacyjnych. Odtąd zachowanie stabilności środowiska wewnętrznego wymaga działania SPA. W przeciwnym razie narasta negatywna emocjonalność (*negative affect*), czyli nieprzyjemne uczucia, takie jak na przykład lęk. Promowane są więc zachowania ukierunkowane na używanie SPA. Według teorii negatywnego wzmacniania (*negative reinforcement theories*) negatywna emocjonalność pełni istotną rolę w rozwoju uzależnienia (12, 13). Przykładem niech będzie model Koob'a (14, 15). Autor ten postuluje, że powtarzające się używanie SPA prowadzi do dysregulacji allostatycznej, która wraz z narastaniem negatywnej emocjonalności przyczynia się do rozwoju uzależnienia. W eksperymentalnych badaniach neurobiologicznych potwierdzono istotną rolę korowych ośrodków

[1] W literaturze panuje pewnego rodzaju chaos pojęciowy, ponieważ zdarza się, że pojęcia *dokładności*, *wrażliwości* i *świadomości interoceptywnej* stosowane są wymiennie. W nowszych pracach użycie tych określeń jest bardziej precyzyjne.

interoceptywnych w uzależnieniach (16). Opisano na przykład strukturalne i funkcjonalne zmiany w obrębie kory wyspy u osób uzależnionych od różnych SPA. Wykazano również odrębności w funkcjonowaniu innych regionów OUN zaangażowanych w przetwarzanie interoceptywne (np. kory przedniej części zakrętu obręczy) u tych osób. Pomimo tego, niewiele jest badań poświęconych ocenie zdolności interoceptywnych w populacjach pacjentów uzależnionych.

Podobnie jest w przypadku alkoholu. Intoksykacja etanolem wywołuje zmiany w ciele, a jego regularne używanie może prowadzić do dysregulacji allostatycznej i w konsekwencji narastania negatywnej emocjonalności. Co ciekawe, Schuckit (17) pokazał w swoich badaniach, że ludzie mogą różnić się w subiektywnej ocenie zmian cielesnych jakie wywołuje u nich użycie alkoholu. Przeprowadzone badania sugerują, że osoby, które słabiej odczuwają wpływ alkoholu na ciało charakteryzują się zwiększonym ryzykiem rozwoju uzależnienia. A zatem można uznać, że zdolności interoceptywne mogą wpływać na percepcję działania etanolu i pośrednio wpływać na ryzyko uzależnienia. Zaburzenie w zakresie prawidłowego odczytywania sygnałów napływających z ciała może także sprzyjać rozwojowi UA poprzez związki interocepcji z czynnikami ryzyka UA takimi jak na przykład impulsywność (18) czy - szeroko dyskutowana w literaturze jako związana z niską interoceptywnością - dysregulacja emocjonalna (19). Z drugiej strony przewlekłe używanie alkoholu może wpływać negatywnie na zdolności interoceptywne. U osób uzależnionych od alkoholu opisywano strukturalne i funkcjonalne zmiany w obrębie kory wyspowej (20, 21). Polineuropatia związana z uzależnieniem od alkoholu wiąże się z uszkodzeniem struktur autonomicznego układu nerwowego, które zaangażowane są w odbieranie i transdukcję sygnałów wzbudzonych w ciele (22). A zatem zależność między interocepcją a używaniem alkoholu jest dwukierunkowa.

Ocena zdolności interoceptywnych była dotychczas przedmiotem niewielu badań w populacji osób z rozpoznaniem UA. W dostępnych, nielicznych pracach skupiano się na prostej ocenie poszczególnych domen interocepcji w tej grupie osób. Wykazano, że pacjenci z UA charakteryzują się zmniejszoną dokładnością interoceptywną (23-25) i jednocześnie zwiększoną wrażliwością interoceptywną w porównaniu z populacją osób bez uzależnienia (23). Postulowano, że ta dysproporcja może być związana z negatywną emocjonalnością. W niniejszej dysertacji podjęto próbę analizy zależności pomiędzy interocepcją a aleksytymią i bólem, czyli czynnikami ryzyka UA, których potencjalne fizjologiczne aspekty są najszerzej opisane w literaturze.

Aleksytymia to niezdolność do rozpoznawania i nazywania własnych stanów emocjonalnych (26). Wykazano, że jest ona związana z negatywną emocjonalnością (27), a

alkohol może być wykorzystywany przez osoby doświadczające tego typu trudności jako strategia radzenia sobie (28). Teza, że większe nasilenie aleksytymii wiąże się z wyższym ryzykiem uzależniania od alkoholu została wielokrotnie potwierdzona (29). Problem może dotyczyć nawet 67% osób z UA (29). Jednocześnie istnieją badania, w których sugeruje się związek aleksytymii z zaburzeniami przetwarzania sygnałów z wnętrza ciała. Niektórzy badacze określają nawet aleksytymię mianem „ogólnego deficytu interocepcji" (30). Wyniki badań neuroobrazowych wskazują na powiązania pomiędzy aleksytymią a interocepcją na poziomie neurobiologicznym (31). Niestety wyniki prac oceniających domeny interocepcji u zdrowych osób doświadczających trudności w opisywaniu swoich stanów wewnętrznych nie są jednoznaczne. Niektóre z nich potwierdzają związki między zmiennymi, a inne dają przeciwne rezultaty. W jednej z ostatnich metaanaliz nie stwierdzono związku pomiędzy dokładnością interoceptywną a aleksytymią (32). Jednakże dostępne dane pokazują, że w populacji osób z UA taka zależność może być istotna. W jednym z badań wykazano, że dokładność interoceptywna może być ujemnie skorelowana z nasileniem aleksytymii w tej grupie (25).

Przewlekły ból jest powszechnym problemem w populacji osób uzależnionych od alkoholu (33). UA bywa nawet niekiedy rozumiane jako „przewlekłe zaburzenie bólowe" (34). Wynika to z neurobiologicznych i genetycznych powiązań pomiędzy tymi zjawiskami. W literaturze zwraca się uwagę na potrzebę badania związków między bólem a UA. Ból, kojarzony tradycyjnie z czuciem eksteroceptywnym, uznawany jest za jedno z podstawowych zjawisk interoceptywnych (35). Jak zauważa Craig, sygnał nocyceptywny przetwarzany jest w układzie nerwowym tak jak inne bodźce interoceptywne. Wykazano, że wrażliwość na ból jest dodatnio skorelowana z dokładnością interoceptywną (36). Stwierdzono również, że pacjenci z rozpoznaniem chorób przebiegających z przewlekłym bólem (np. fibromialgia) cechują się gorszą dokładnością interoceptywną (37). Co zaskakujące, zależności pomiędzy bólem a interocepcją w populacji pacjentów z rozpoznaniem UA nie były dotychczas badane.

Analiza literatury przedmiotu pozwala stwierdzić, że interocepcja może pełnić istotną rolę w UA. Jednocześnie niewiele jest badań, w których podejmuje się ten temat. Cykl artykułów składających się na niniejszą rozprawę ma służyć poszerzeniu wiedzy w tym zakresie. Poświęcony jest on ocenie zdolności interoceptywnych u pacjentów uzależnionych od alkoholu z uwzględnieniem innych, istotnych dla tej grupy zmiennych tj. przede wszystkim aleksytymii i bólu. Zależności pomiędzy tymi zmiennymi wydają się być teoretycznie uzasadnione. Alkohol pozwala redukować nieprzyjemne stany związane z negatywną emocjonalnością (np. lękiem) czy bólem. Jedocześnie ma bezpośredni wpływ na ciało, zaburza

jego wewnętrzną stabilność, a w dłuższej perspektywie prowadzi do stałych patofizjologicznych zmian. To właśnie z uwagi na te biologiczne zmiany, które alkohol wywołuje w ciele w ocenie interocepcji wykorzystano mierzoną behawioralnie dokładność interoceptywną (*interoceptive accuracy*). Wspomniane już teorie emocji pozwalają podejrzewać, że u podłoża aleksytymii może leżeć nieprawidłowe przetwarzanie zmian zachodzących w środowisku wewnętrznym. Ból uznawany jest za jedno z podstawowych odczuć interoceptywnych. Zarówno aleksytymia, jak i przewlekły ból, są związane z nasileniem negatywnej emocjonalności. Ta z kolei, związana jest ze zwiększonym ryzykiem UA.

Cykl publikacji składających się na tę rozprawę obejmuje badania dotyczące zgodnej tematyki – ocenę zdolności interoceptywnych u osób uzależnionych od alkoholu z uwzględnieniem zmiennych będących czynnikami ryzyka tego uzależnienia. W pierwszej publikacji zawarto dokładny przegląd literatury dotyczący aktualnego stanu wiedzy na temat związków pomiędzy interocepcją a problemowym używaniem alkoholu. W kolejnych pracach opisano badania dotyczące związków pomiędzy interoceptywnością, aleksytymią, bólem i nasileniem lęku w grupie osób zdrowych i uzależnionych od alkoholu. Całość stanowi zatem wszechstronny opis zależności pomiędzy zdolnością do odczytywania sygnałów napływających z wnętrza ciała a innymi zmiennym ważnymi w rozwoju i przebiegu UA. Podjęte badania wydają się uzupełniać zidentyfikowane luki w aktualnym stanie wiedzy, a dodatkowo mogą mieć znaczenie kliniczne poprzez wpływ na usprawnienie programów leczenia, których dotychczasowe wyniki nie są satysfakcjonujące. Praca nad poprawą zdolności interoceptywnych może stanowić ważny cel terapeutyczny.

Założenia i cel pracy

Celem ogólnym pracy była ocena dokładności interoceptywnej u osób uzależnionych od alkoholu oraz analiza zależności pomiędzy dokładnością interoceptywną a innymi, uznanymi czynnikami ryzyka rozwoju i ciężkiego przebiegu UA: aleksytymią, negatywną emocjonalnością i wrażliwością na ból.

Cele szczegółowe i hipotezy:

Cel 1:
Porównanie dokładności interoceptywnej między grupą osób z rozpoznaniem UA a grupą osób zdrowych.

Hipoteza 1:
Osoby z rozpoznaniem UA będą charakteryzowały się gorszą dokładnością interoceptywną niż osoby zdrowe.

Ad 1:

Jak opisano wyżej, zależność między interocepcją a UA jest dwukierunkowa. Zaburzenia w zakresie przetwarzania sygnałów napływających z ciała mogą sprzyjać rozwojowi uzależnienia, na co mogą wskazywać związki interocepcji ze zidentyfikowanymi czynnikami ryzyka uzależnienia od alkoholu jak na przykład impulsywnością czy zaburzeniem regulacji emocji (18). Przewlekłe używanie alkoholu negatywnie wpływa na zdolności interoceptywne w wyniku uszkadzającego wpływu na układ interoceptywny (20, 21). Uzasadnione wydaje się zatem założenie, że osoby z rozpoznaniem UA powinny charakteryzować się gorszą dokładnością interoceptywną niż osoby zdrowe. Dotychczasowe badania potwierdziły taką zależność, ale były prowadzone na małych grupach badawczych (23-25).

Cel 2:
Ocena zależności pomiędzy dokładnością interoceptywną, aleksytymią i negatywną emocjonalnością (lękiem) w grupie osób z rozpoznaniem UA.

Hipoteza 2.1:

Gorsza dokładność interoceptywna będzie związana z istotnie wyższą aleksytymią i większą negatywną emocjonalnością (lękiem) w grupie osób z rozpoznaniem UA.

Hipoteza 2.2

Aleksytymia będzie mediatorem relacji pomiędzy dokładnością interoceptywną a negatywną emocjonalnością (lękiem) w grupie osób z rozpoznaniem UA.

Ad 2:

Alkohol używany bywa jako sposób radzenia sobie z nieprzyjemnymi stanami emocjonalnymi, jak na przykład lęk, rozdrażnienie czy smutek (tj. negatywna emocjonalność). Teorie negatywnego wzmacniania podkreślają ważną rolę jaką proces ten pełni w rozwoju uzależnienia (12, 15). Przykładem może być model allostatycznej dysregulacji Koob'a, który opisuje uzależnienie jako cykl oparty na mechanizmach zarówno pozytywnego, jak i negatywnego wzmocnienia (15). Wśród istotnych źródeł negatywnej emocjonalności autor wymienia aleksytymię. Badania empiryczne potwierdzają związek pomiędzy trudnościami w rozpoznawaniu własnych stanów emocjonalnych a negatywną emocjonalnością (w tym lękiem) (27). Nie brakuje również literatury wiążącej aleksytymię z nieprawidłowym używaniem alkoholu (29). Cruise i Beccera stwierdzają nawet, że aleksytymię należy uznać za niezależny czynnik ryzyka UA (38). Podaje się, że od 30 do 67% populacji osób uzależnionych od alkoholu może mieć trudności w rozpoznawaniu swoich stanów emocjonalnych (29, 38). Aleksytymię powiązano z wcześniejszym wiekiem rozpoczęcia używania alkoholu, dłuższym czasem problemowego używania alkoholu (39) i większym ryzykiem nawrotu (40). Dodatkowo niekorzystny wpływ używania alkoholu na zdolności interoceptywne może nasilać trudności w nazywaniu własnych emocji, a przez to wzmagać nasilenie negatywnych stanów emocjonalnych. U podłoża trudności z rozpoznawaniem własnych stanów emocjonalnych może leżeć z kolei zaburzenie interocepcji. Tego typu rozumowanie ma swoje źródło we wspomnianych już teoriach emocji, które uznawały sygnały napływające z wnętrza ciała za kluczowe dla rozpoznawania i różnicowania stanów emocjonalnych. W niektórych współczesnych konceptualizacjach aleksytymię bezpośrednio wiąże się z zaburzeniem interocepcji (30, 41). Jednakże dostępne w literaturze dane z badań empirycznych dotyczących związków pomiędzy aleksytymią a interocepcją nie są jednoznaczne (32). Podobnie niejednoznaczne wyniki dają badania bezpośrednich związków pomiędzy interocepcją a negatywną emocjonalnością. W jednej z ostatnich metaanaliz nie znaleziono powiązań między

dokładnością interoceptywną a lękiem u osób zdrowych (42). Inaczej zależności te mogą wyglądać w odniesieniu do osób uzależnionych od alkoholu. W dostępnych badaniach wykazano, że osoby z UA gorzej przetwarzające sygnały interoceptywne mogą charakteryzować się wyższym poziomem lęku (23).

Analiza dotychczasowych danych pokazuje, że negatywna emocjonalność, aleksytymia i interocepcja mogą mieć niebagatelne znaczenie w rozwoju i podtrzymywaniu uzależnienia od alkoholu. Nie ma jednak badań poświęconych wzajemnym zależnościom między tymi czynnikami. Na podstawie dostępnych danych przyjęto, że osoby z rozpoznaniem UA gorzej przetwarzające sygnały interoceptywne będą charakteryzowały się większymi trudnościami w zakresie rozpoznawania własnych emocji i wyższym nasileniem lęku. Uznano dalej, że u podłoża aleksytymii będącej źródłem negatywnej emocjonalności mogą leżeć zaburzenia w zakresie zdolności interoceptywnych. Sformułowano więc hipotezę, według której aleksytymia będzie mediatorem relacji pomiędzy dokładnością interoceptywną a lękiem (negatywna emocjonalność). Przyjęto, że zdolność do prawidłowego odczytywania sygnałów napływających z ciała należy uznać za zjawisko pierwotne wobec rozpoznawania emocji, stąd rolę mediatora przypisano aleksytymii. Ocena tych zależności może mieć duże znaczenie kliniczne w kontekście poszukiwania nowych celów terapeutycznych dla osób uzależnionych od alkoholu.

Cel 3:

Ocena związków pomiędzy dokładnością interoceptywną i wrażliwością na ból w grupie osób z rozpoznaniem UA i grupie kontrolnej osób zdrowych.

Hipoteza 3:

W grupie osób z rozpoznaniem UA gorsza dokładność interoceptywna będzie istotnie związana z większą wrażliwością na ból, a w grupie kontrolnej osób zdrowych obserwowana będzie odwrotna zależność.

Ad 3:

Używanie alkoholu jest również jedną ze strategii radzenia sobie z bólem (43). Potwierdzono, że przewlekły ból może przyczyniać się do rozwoju uzależnienia od alkoholu (44). Osoby z rozpoznaniem tego typu uzależnienia często (~35%) relacjonują występowanie przewlekłego bólu (33). Ból może mieć także niekorzystny wpływ na leczenie uzależnienia (wykazywano, że im większe nasilenie bólu, tym większe ryzyko nawrotu) (43). Ponadto

przewlekłe używanie alkoholu prowadzić może do rozwoju zaburzeń związanych z bólem (np. polineuropatia) (45). Istnieje wiele wzajemnych powiązań pomiędzy bólem a uzależnieniem od alkoholu na poziomie neurobiologicznym czy genetycznym, które wykraczają poza analgetyczny efekt etanolu (34). W tym kontekście wydaje się szczególnie interesujące, że Craig, jeden z głównych badaczy interocepcji, wymienia ból wśród odczuć interoceptywnych (3). Swoje stanowisko tłumaczy obserwacją, że sygnał bólowy przetwarzany jest w ośrodkowym układzie nerwowym dokładnie tak, jak przetwarzane są inne bodźce interoceptywne. Co więcej autor ten określa ból „homeostatyczną emocją" wskazując na jego motywacyjny wpływ na zachowanie (46).

Wobec powyższych rozważań uzasadnione wydaje się poszerzanie wiedzy na temat wzajemnych relacji pomiędzy interocepcją i bólem. W nielicznych badaniach analizujących związki między tymi czynnikami w populacji osób zdrowych wykazano, że dokładność interoceptywna jest w tej grupie dodatnio skorelowana z wrażliwością na ból (47). Co ciekawe populacje pacjentów doświadczających przewlekłego bólu charakteryzują się zmniejszoną dokładnością interoceptywną (37). W literaturze brakuje badań analizujących związki między interocepcją i bólem u pacjentów z rozpoznaniem UA. Biorąc pod uwagę dotychczasową wiedzę na temat znaczenia tych czynników w rozwoju uzależnienia oraz wzajemnych powiązań między nimi, ten kierunek badań wydaje się zaniedbany. Zarówno zaburzenia interocepcji, jak i ból mogą przyczyniać się do rozwoju uzależnienia. Dodatkowo z dostępnych danych wynika, że pacjenci z rozpoznaniem uzależnienia od alkoholu charakteryzują się zmniejszoną dokładnością interoceptywną przy zwiększonej wrażliwości interoceptywnej (23). Rozpatrując uzależnienie od alkoholu jako przewlekłe zaburzenie bólowe, a ból jako doznanie interoceptywne, sformułowano hipotezę, według której w populacji pacjentów uzależnionych od alkoholu dokładność interoceptywna będzie ujemnie korelować z wrażliwością na ból.

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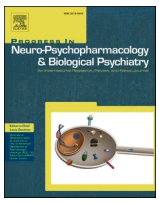

Alcohol use and interoception – A narrative review

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ABSTRACT

Interoception, defined as the ability to perceive and interpret body signals, may play an important role in alcohol use disorder (AUD). Earlier studies suggested an association between interoception impairment and known risk factors for AUD (e.g., alexithymia, emotion dysregulation, impulsivity, pain). Neurobiological studies show that the neurotoxicity of alcohol affects various elements of the interoceptive system (especially the insula) at structural and functional levels, with differential short/long term impacts. Conversely, primary interoceptive impairments may promote alcohol consumption and foster the evolution towards addiction. Despite convincing evidence demonstrating that interoception impairment may be an important contributor to the development and course of AUD, only a few studies directly evaluated interoceptive abilities in AUD. The research shows that interoceptive accuracy, the objective component of interoception, is lower in AUD individuals, and is correlated with craving and emotion dysregulation. Interoceptive sensibility is in turn higher in AUD individuals compared to healthy controls. Moreover, there is evidence that therapy focused on improving the ability to sense signals from the body in addiction treatment is effective. However, important methodological limitations in interoceptive measures persist, and it is therefore necessary to further investigate the associations between interoception and AUD.

1. Introduction

Interoception is conceptualized as a combination of processes that reflect the perception of body signals, their processing by the central nervous system, and the development of associated mental representations (29, 32). Deficits in interoception have been well documented in a broad range of psychiatric disorders (79, 101) with some studies notably suggesting the presence of interoception impairments in addictive disorders.

The aim of this review is to present neurobiological and psychological findings indicating the significance of interoceptive processes among problematic alcohol users. This review is organized in two sections: (1) a summary of the current understanding of interoception and of its relevance for psychology and health, with particular emphasis on addictive behaviors (especially alcohol use disorder [AUD] and its risk factors); (2) an overview of the knowledge about the effects of alcohol on various functional elements of the interoceptive system (primarily the insula) and a summary of the existing research on the different domains of interoception among individuals with AUD. The manuscript extends ideas already suggested in previous literature reviews [57,63,64], with a special focus on severe AUD (while previous reviews mostly focused on subclinical patterns of excessive alcohol consumption).

PART 1.

2. INTEROCEPTION and related impairments

2.1. The concept of interoception

The view of interoception has changed significantly since 1906, when Sherrington first used this concept by focusing solely on the biological aspects of receiving signals from the body (129). More recently, a broader view of this phenomenon emerged following strong evidence indicating the involvement of interoception in psychological processes

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associated with behavioral regulation (for a review see 20). The link between signals arising from the body and emotional feelings has its origin in the nineteenth century theory of emotions formulated independently by James and Lange (85). They postulated that the experience of emotions is preceded by physiological arousal. In recent years, researchers have studied the role of interoception in the relationship between body and mind. Consequently, the importance of interoception is now recognized in emotion (32), cognition (58, 140), and self-awareness (embodiment theories; 125). Recent theories suggest a more complex conceptualization of interoception, in which it is defined as the process of *bidirectional* interactions between the brain and other organs that enable sensing, integration, and regulation of internal states (see 21 for review).

Three basic domains of interoception have been identified in humans: (1) interoceptive accuracy (also known as interoceptive sensitivity) reflects the objective component of interoception; (2) interoceptive sensibility reflects the subjective component, and (3) interoceptive awareness reflects metacognitive confidence in detecting signals from the body (50). Importantly, research on anxiety disorders (42) and AUD (73) demonstrates that interoceptive accuracy (sensitivity) is independent of interoceptive sensibility. While interoceptive sensibility is assessed via self-report measures, interoceptive accuracy requires behavioral testing. Given the multimodal nature of interoception and the fact that interoceptive signals likely emerge from different areas of the body, studies distinguish several modalities of interoception, such as cardiac, gastric, and respiratory. While self-report measures can investigate several modalities simultaneously, behavioral tests examine only one at a time. Cardioception is by far the most studied modality in interoception research, with the most widely used behavioral test being the heartbeat counting task (Schandry Test; 121). The task requires participants to assess their cardiac rhythm (i.e., number of heartbeats) during specific time intervals without relying on external cues. In recent years, however, there has been a discussion regarding the use of heartbeat counting in interoception research, as an increasing number of methodological shortcomings have been noted (see 154 for more details). Despite these limitations the Schandry Test remains the most widely used measure in interoception research (see 157). Nevertheless, given the multidimensional nature of interoception, it is important to note that other behavioral tests have been developed to assess other modalities within the cardiac domain (e.g., Heartbeat Detection Task), as well as the gastric (e.g., Water Load Test and its modifications), respiratory (e.g., Respiratory Detection Task, Respiratory Discrimination Task), and tactile (Soft Touch Task) domains. Yet, these behavioral tests are rarely used, particularly within AUD samples. Given the increased attention on multimodal approaches in the assessment of interoceptive accuracy, future work in this area, especially as it relates to the development of alternative interoception measures (e.g., 142), will significantly advance the field.

2.2. Neurobiology of interoception – The interoceptive system

Neurobiological knowledge on interoception has expanded recently. Craig (29) presented a detailed description of the interoceptive pathway, recognizing it as the missing sympathetic afferent pathway of the autonomic nervous system. Commonly found in almost all tissues, small diameter fibers (A- and C-fibers), which are free endings of axons, collect information about the current physiological condition of the body and transmit it to the neurons of the most superficial layer of the spinal dorsal horn (lamina I). In turn, these neurons project to the basal and posterior parts of the ventral medial nucleus of the thalamus. The information is subsequently transmitted to the posterior insular cortex, where the interoceptive representation of the physiological state of the body is built. The re-representation of this region in the right anterior insula is crucial for the subjective awareness of emotion. The insular cortex presents structural and functional specificities. The posterior part of the insula encodes the primary physiological states of the body (homeostatic or allostatic states), while its anterior part is responsible for encoding cognitively and emotionally processed bodily states (31). Previous research has recognized the high importance of the insula in sensorimotor, emotional and cognitive processes, as well as in multidimensional models reflecting a combination of these processes, especially with regard to pain or decision making (141). The anatomical basis of interoception is completed by the long-known parasympathetic pathway with its afferents projecting to the anterior insula via the nucleus of the solitary tract in the brainstem. The parasympathetic activity is then re-represented, in contrast to the sympathetic pathway, in the left anterior insula (29-31). Subsequently, the interoceptive signal is transmitted to higher cortical centers of the brain, where integration of internal signals with exteroceptive, cognitive, and emotional information take place (for a review see 21).

As a whole, efficient interoceptive processes rely on a network of subcortical and cortical areas, below (e.g., the thalamus) and beyond (i.e., anterior cingulate cortex, orbitofrontal and medial prefrontal cortices, but also primary and secondary somatosensory cortex) the insula. Nevertheless, the central role played by the insula in interoception has been largely documented, in healthy populations (e.g.,21) as well as in clinical samples (e.g., 112). Accordingly, the insula is widely considered a hub for interoception with insular dysfunction believed to be at the heart of interoceptive deficits among individuals with substance use disorders (e.g., 146). In view of this key role, the insula will be the central brain structure considered in the present review, keeping in mind that, as previously, it is part of a larger interoceptive brain network.

2.3. Interoception and psychopathology related to AUD

James and Lange hypothesized that emotional stimulus causes various physiological changes in the body that can affect the emotional experience (85). Damasio later stated that these physiological changes must have their neural representations and that “somatic markers” play an important role in generating and carrying emotional states, further affecting cognition and behavior (35). Contemporary embodiment theories refined these views even further by recognizing that conscious experience of emotions requires operating on perceptual symbols (i.e., (re-)representations of the somato-motor and visceral states) that are activated when experiencing a particular emotional feeling or even when thinking about emotions (106). Given that the interoceptive system is paramount in both experiencing the current physiological state of the body and creating its mental representation, which are critical for conscious emotional feelings and emotion regulation, it plays a key role in influencing behavior.

These observations may be important in the context of AUDs. Based on the James-Lange theory of emotions and Damasio’s somatic marker hypothesis, as well as research on addiction in general, it follows that the disturbances in interoceptive processes may be significant in the context of emotional, cognitive, and behavioral alterations associated with alcohol use. Namely, prior work indicates that interoception plays an important role in psychopathological phenomena that are risk factors for AUD such as alexithymia (101), emotional dysregulation (49), impulsivity (62) and pain (132) (Fig. 1).

2.3.1. Alexithymia

Alexithymia is defined as an impairment of recognition and description of one’s own emotional states at the affective and cognitive levels (136). More recent research proposes a broader definition of alexithymia as it can also apply to non-affective interoceptive states (15). Current theoretical models of alexithymia associate difficulties in identifying emotions with reduced interoceptive abilities (101), while psychological and neurobiological empirical studies support a mutual association between these constructs underscoring the link between bodily and emotional awareness. Still, more recent studies suggest that these associations are complex and nonlinear (1). Among findings that

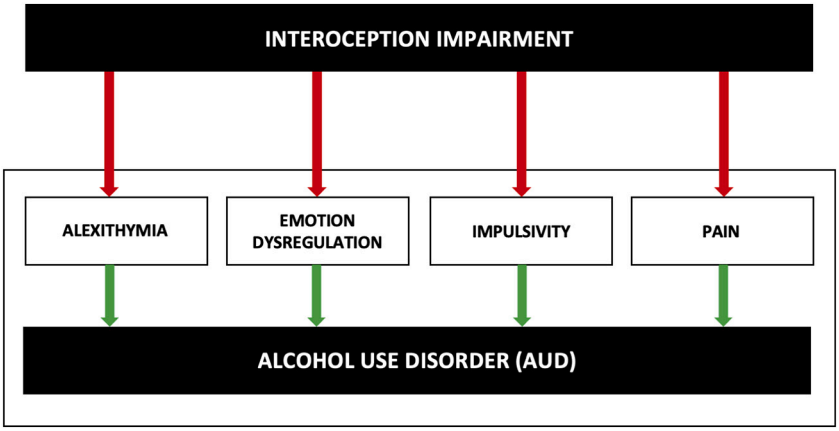

Fig. 1. Interoception impairment can affect known risk factors for AUD. Primary disturbances in interoceptive processes may affect alexithymia, emotion dysregulation, impulsivity or pain and, as a result, contribute to AUD.

offer conflicting evidence regarding the association between alexithymia and interoception (1,14,15,61,89,126,155), one meta-analysis concluded that lower interoceptive sensibility is associated with problems in identifying emotions, and that this association is stronger among individuals with co-occurring psychiatric disorders than in healthy participants (139). These findings suggest that inconsistent results across prior studies may be largely due to differences in assessments. Namely, because alexithymia is only measured via self-report, the association is stronger with self-reported interoceptive sensibility than with the experimentally measured interoceptive accuracy. At the neurobiological level, there are common elements between interoception and alexithymia. New data recently revealed that high alexithymia might be a consequence of a multi-domain failure of interoception related to functional, structural, and neurochemical integrity of the anterior insular cortex (12,102). A meta-analytical study on brain's structural abnormalities associated with alexithymia showed smaller grey matter volume of the insula (especially the anterior insula) among participants with alexithymia (151). The abnormal function of the insula was also confirmed in meta-analytic neuroimaging studies among individuals with alexithymia (143).

2.3.2. *Emotion dysregulation*

Interoception is not only a significant prerequisite for emotion identification but also for proper *emotion regulation*. Since body-relevant signals provide information about the organism's arousal, it has been proposed that interoception is crucial for the processing of emotional states and their regulation (49). Greater accuracy in sensing one's bodily state may facilitate the regulation of emotional responses, as ongoing bodily changes can be detected more accurately (29). Greater interoceptive accuracy was found to be a positive precondition for effective self-regulation of emotionally driven behavior in healthy individuals (49). According to Gross, emotion regulation is an adaptive ability to modulate the experience of emotion in order to achieve a specific goal in a specific context (56). Psychological and neurobiological studies indicate that interoception is an important contributor to the process of emotion regulation. The ability to recognize physiological states of the body allows for better emotion regulation accompanying everyday events (153). Interoceptive accuracy is positively correlated with emotion regulation strategies (cognitive reappraisal and expressive suppression), and individuals with higher interoceptive accuracy are more accurate in matching an effective emotion regulation strategy to a specific context (78). For example, they are more likely to choose a cognitive reappraisal strategy (49), which is considered to be more adaptive than available alternatives to regulate emotion (33). At the neurobiological level, the important function of the insula in the process of emotion regulation has been established. A recent meta-analysis examining neural activity when adopting different emotion regulation strategies concluded that the insula is one of the three brain regions (along with the ventrolateral prefrontal cortex and the supplementary motor area) that is active across multiple regulation strategies (e.g., cognitive reappraisal, expressive suppression, distraction, detachment; 99). Upon further analysis, it was proposed that the anterior insula controls the activity of other brain regions by acting as an "outflow hub", initiating and adjusting cognitive control mechanisms involved in emotion regulation (99). Recent research indicates that different parts of the insula may have different functions in emotion regulation. Primary emotional states activate the posterior part of the insula. As the emotional state is regulated based on additional cognitive information, the frontal parts of the insula become more involved in the process (156).

2.3.3. *Impulsivity*

Impulsivity, a multi-dimensional concept, is another risk factor for AUD that is associated with emotional and interoceptive processing. Research distinguishes impulsivity as a personality trait (measured by self-report measures) that increases risk for rapid and unplanned behaviors without considering possible negative consequences (97) from its behavioral representation reflected in the decision-making process: (1) reflection impulsivity ("too fast decision"), (2) motor impulsivity ("too fast action") and (3) temporal impulsivity ("too long for gratification") (62). Due to the multimodal nature of impulsivity, many theories based on neurobiological findings regarding key neural circuits have been proposed. However, it should be noted that in most of these studies a large role is assigned to the central part of the interoceptive system - the insula. Neuroimaging studies confirm the significant role of the insula in motor impulsivity (36), temporal impulsivity (47), and reflection impulsivity (48). Interestingly, a strong association between the structure of the insula and impulsivity has also been demonstrated in animal studies (7). Therefore, it is likely that circuits involved in interoception and impulsivity overlap. Psychological studies investigating the association between impulsivity and interoception indicate that high impulsivity is associated with interoceptive impairment (62).

2.3.4. *Pain*

According to Craig's research, *pain* is an interoceptive feeling that is processed via interoceptive pathways (29), as well as a homeostatic emotion that may motivate behavior (30). Experimental neurobiological research confirms the overlap between brain regions associated with pain and those related to interoception (17). There is behavioral evidence for impaired interoceptive processing among individuals experiencing chronic pain. Data show that individuals with chronic pain are characterized by decreased interoceptive accuracy (132) that correlates

negatively with pain severity (41). In addition, the positive correlation between interoceptive accuracy and pain sensitivity has been shown among healthy individuals (116, 148). Pain-related negative affectivity may impair interoceptive accuracy, suggesting that the affective aspects of pain influence the perception of internal bodily signals (13). Indeed, recent studies highlight the association between pain and emotions at neurobiological and psychological levels (90), suggesting that pain is a more complex construct than just nociception (52).

PART 2.

3. INTEROCEPTION and alcohol

3.1. Theoretical accounts

In recent years, several theories have emerged, indicating the importance of interoceptive signals in addictive behaviors (including those related to AUD). In the context of interoception, three of them seem particularly relevant.

Paulus and colleagues (114) introduced a model supporting the critical role of the central part of the interoceptive system – the insula – has in addiction. They posit that addiction represents an internal dysregulation caused by a body prediction error alteration (the disparity between anticipated and current interoceptive states) that leads to a disturbance in interoceptive regulatory mechanisms. In this model, drugs of abuse disturb homeostasis through numerous internal body changes. Long-term repeated allostatic dysregulation caused by drugs affect internal states centrally generated in the insula. The abnormal function of the insula leads to maladaptive adjustment of the body prediction error and results in an unstable aversive state of the organism. As a consequence, these changes tend to favor addictive behaviors (114).

The model of allostatic dysregulation proposed by Koob and colleagues is of particular interest in terms of the potential contribution of interoception. In this model, allostatic dysregulation caused by repeated drug use (initially driven by pleasure) leads to the emergence of negative affect (withdrawal symptoms) and consequently converts the use of drugs from an impulsive to a compulsive mode of action (negative reinforcement) (82). The researchers identified three stages of addiction: (1) the binge/intoxication stage, (2) the withdrawal/negative affect stage, and (3) the preoccupation/anticipation stage. They indicate the role of the insula and its connections at every stage (84). The peripheral part of the interoceptive system may be of great importance in primary homeostatic dysregulation by establishing new allostatic set points in this model.

The triadic neurocognitive model of addiction presented by Noël and colleagues assumes the impaired functioning of three interrelated neural systems: (1) the impulsive system – amygdala-striatum dependent neural circuits responsible for automatic salient behaviors (traditional reward system), (2) the reflective system – prefrontal cortex dependent system responsible for predicting consequences of a behavior, and (3) the insular cortex – responsible for mental representation of interoceptive states. The authors emphasize the importance of the insula in a disturbed decision-making process leading to the development and maintenance of addiction. During drug use, the insula sensitizes the impulsive system and inhibits the reflective system by altering interoceptive processing to maintain homeostasis through the reduction of conflicting signals associated with motivation (reward) and withdrawal (107).

There are several experimental studies that support theories linking addiction with interoception. Naqvi and Bechara noted the importance of interoceptive signals in addictive behaviors. Through their research, they found the critical role of insular damage on the course of nicotine addiction among stroke survivors. Namely, they observed that the urge to smoke was significantly reduced among those whose insula was damaged as a result of a stroke (105). The results were then reaffirmed in studies on rats whereby animals in which the function of the insula was disturbed demonstrated reductions in drug use behavior that was previously conditioned (27). Based on these observations along with support from other data, the researchers stated that the insula plays a key role in encoding emotional representations from drug-related interoceptive signals (e.g., the taste of alcohol or the sympathomimetic effects of cocaine), which gain positive value through a learning process. According to their hypothesis, these representations may contribute to the conscious feeling of drug urges and the ultimate decision to use substances when exposed to external drug cues among individuals engaged in problematic substance use (103). Many studies indicate the dysfunction of the interoceptive system in addiction-related behaviors at the neurobiological level (146). The research focuses primarily on the important role of the insula in these processes (104). Neurobiological studies on the role of interoception in substance use populations show structural and functional abnormalities of the insula in individuals with amphetamine (92), cocaine (76), and cannabis use disorder (72). In their meta-analysis, Pando-Naude and colleagues (111) determined that the insula and other brain regions (i.e., anterior cingulate cortex, thalamus, putamen) evidenced the most structural impairment (lower grey matter volume) among individuals with substance use disorders relative to controls. The changes appeared to be mostly independent from the substance used. There is also evidence for shared functional abnormalities of the insula in individuals with substance use disorders that are more substance specific. Namely, reduced insular cortex activity during decision-making tasks was found among those with a methamphetamine or cannabis use disorder, while reduced insular cortex activity during evaluative tasks was found among those with a methamphetamine, nicotine, and alcohol use disorder in comparison to healthy controls (43). Similarly, a recent meta-analysis of neuroimaging studies in substance use disorders (nicotine, cocaine, cannabis, and alcohol) show substance-specific insular function alterations, but the specific results are beyond the scope of this review (see 80 for more details).

These data show that the interoceptive system may play a crucial role in the development and course of addiction. Unfortunately, only a few studies have assessed the multiple domains of interoception (interoceptive accuracy and/or interoceptive sensibility) among individuals with substance use disorder. Preliminary data exist among cocaine users (38), nicotine smokers (66), and individuals with AUD (73). Recent studies support these observations and suggest differences in interoceptive processing in individuals with substance use disorders relative to healthy controls, such as impaired flexibility (less perceptual sensitivity to the interoceptive signals' modulations) (130,131). Therefore, interoceptive processing in individuals with substance use disorders warrants further investigation.

3.2. Neurobiological basis: Alcohol

The link between problematic alcohol use and interoception should be considered at several levels. First, it is important to distinguish between the effects of alcohol intoxication on the perception of bodily signals (e.g., by disrupting the functioning of brain structures important for interoception) and the long-term effects of alcohol use on the interoceptive system (alcohol consumption leads to deficits). Secondly, apart from the changes related to alcohol, it should be noted that some primary interoceptive impairments (e.g., neurobiological changes and psychological characteristics) may promote alcohol consumption leading to addiction (deficits lead to alcohol consumption) (Fig. 2).

Acute alcohol administration alters interoception. Individuals differ in their subjective assessment of the interoceptive effects associated with alcohol intoxication (123). In this context, a group of individuals with a low level of response to alcohol can be identified. Reduced ability to perceive signals from the body caused by alcohol is associated with an increased risk of addiction in the future (123). Although this characteristic relates to a specific type of interoception (i.e., the perception of the effects that alcohol has on one's body), it suggests that alcohol modifies the way the internal milieu is recognized. Indeed, research

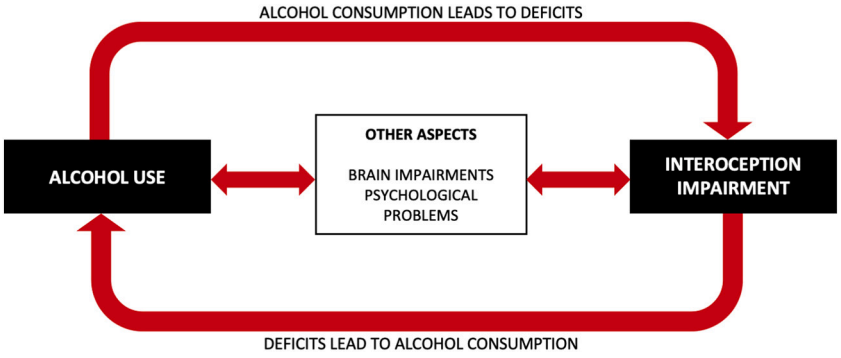

Fig. 2. The association between interoception impairment and alcohol use is bidirectional. Interoceptive deficits can lead to alcohol consumption, for example, by influencing factors such as impulsivity and emotional dysregulation. In turn, alcohol consumption can damage the structures of the interoceptive system and interfere with the processing of signals related to the internal environment. Other aspects, such as organic and psychological disorders, can further influence this cyclical relationship.

shows that alcohol intoxication changes activity of the insular cortex, but the direction of these changes is not clearly established. Decreased insular activity following acute alcohol intoxication may impair decision-making (4,128) and emotional processing (110). Alcohol intoxication may increase risk-taking behavior by activating brain regions including the insula (53).

Long-term excessive alcohol consumption has a more significant influence on the structure and function of the interoceptive system. Current data show that the various structures identified by Craig as key components of the interoceptive system are impaired in individuals misusing alcohol (e.g., 16). Most of the data involves the insula and the evidence for other components of the interoceptive system is weaker.

Many studies revealed the influence of alcohol use and misuse on the insula, a common element for both the sympathetic and parasympathetic pathways of the interoceptive system (e.g., 22,150,160). The most significant changes concern individuals with an alcohol use disorder, but they also affect drinkers who do not meet diagnostic criteria. Two meta-analyses performed recently on studies using voxel-based morphometry to assess grey matter abnormalities among alcohol dependent patients confirmed grey matter atrophy in the bilateral insular cortex and its reduction relative to healthy controls (150,152). Mackey and colleagues showed lower thickness of the insular cortex in individuals with substance use disorder (alcohol, nicotine, cocaine, methamphetamine, or cannabis) with the most substantial effect associated with AUD (91). It appears that there are no differences in alcohol-induced insular cortex atrophy/insular volume decrease between males and females (39,120,137). The right insula volume might be more prone to the synergistic effects of age and alcohol misuse (137). Grey matter atrophy associated with alcohol dependence is partially reversible with abstinence. The insular grey matter volume (19) and its connectivity (100) partially recovers during both short-term and long-term abstinence (158) with some indicating partial recovery within 2 weeks of abstinence (144). The negative impact of alcohol on insular morphology may occur at an early age. Excessive alcohol use among adolescents not meeting AUD criteria was linked to structural changes (decreased grey matter volume) in the right insula (60), and these changes were more substantial than similar changes caused by cannabis use (71). Even young adults who have only experienced hangover symptoms in the past may have similar abnormalities (67).

Morphological abnormalities related to the toxic effects of alcohol can also affect white matter of the central interoceptive system. There are abnormalities in the microstructure of white matter and structural connectivity of the right insula among individuals with AUD (22). Namely, among individuals engaging in heavy alcohol consumption, white matter integrity in frontoparietal and corticolimbic networks is negatively correlated with insular activation (98). The white matter volume of the right insula is positively correlated with craving for alcohol (23).

Functional neuroimaging studies show that both the structure and the functioning of the interoceptive system may be impaired due to alcohol use. That is, increased functional connectivity of the anterior insula may be involved in the maintenance of drinking behavior among individuals with AUD (59). Activation of brain regions involved in the brain reward system, including the insula, is related to cue-induced alcohol craving among individuals with AUD (109). In a study conducted by Strosche and colleagues, abstinent individuals with AUD showed increased functional connectivity of the insula during the presentation of alcohol-related cues and these changes correlated with subjective craving and compulsive use of alcohol (134). Sullivan and colleagues postulated that deficits in the insular blood perfusion in individuals with AUD may impair cognitive control over internal urges (135). Although, the insular response pattern in neuroimaging studies in individuals with AUD is complex, insular activity increases in response to alcohol-related stimuli and decreases when involved in cognitive processes, which is in line with previous observations in other populations with substance use disorder (113). Prior research also supports the influence of alcohol use on the insular function in individuals who do not meet the criteria for AUD (147). The insula is among the main brain areas of the resting state functional network showing connectivity reduction in alcohol users compared to non-substance using controls (147). Resting state insular connectivity patterns also correlate with AUD severity (24).

As mentioned before, some abnormalities in the functioning of the interoceptive system in alcohol-misusing individuals are related to factors that may contribute to the development of addiction (e.g., impulsivity, decision-making impairments). Structural changes of the insula are linked to several behavioral consequences. Volume of the anterior insula was shown to be negatively associated with self-reported impulsivity and compulsivity in individuals with AUD (54). Smaller grey volume of the insula may represent genetically conferred risk factors predisposing individuals to use alcohol (6). Furthermore, a negative correlation between insular grey matter volume and alcohol use severity was demonstrated (11), especially in relation to the middle insula (86). The insula is one of the brain regions which abnormal activation during task performance might contribute to impulsive choice (26), impaired inhibitory control (25) and risk-taking decisions (88) in individuals with AUD. Maurage and colleagues have linked abnormal insular activation in individuals with AUD with interpersonal problems in this group (94). By assessing insular activity while performing a task where inspiratory breathing load was recorded, Berk and colleagues found that adolescents with AUD may be hypersensitive to aversive interoceptive stimuli (9). Abnormal insular activity associated with alcohol withdrawal may underlie impaired emotion processing (increased sensitivity to emotional stress) in individuals with AUD (108). Similar observations were made in healthy controls. That is, greater activation of the anterior insula and other regions of the frontostriatal circuitry was associated with compulsive alcohol seeking (55) and decision-making (3,93) in heavy drinkers. Similarly, the bilateral activation of the insula was related to decision-making in binge drinkers (149). In addition, frontoinsular activity was associated with response inhibition and cognitive control impairment in binge drinkers (28). Anterior insular cortex activation was linked to risk taking in hazardous drinking individuals (26).

The alcohol-related insular functional activity abnormalities may play an important role in fostering future problem drinking. Lower connectivity between the left nucleus accumbens and other regions, including the left insula, in young male adults was associated with higher lifetime alcohol consumption (145). The differences in brain activity in specific regions including the insula between heavy drinkers and non-heavy drinkers exposed to alcohol-related cues may be useful as a pre-diagnostic marker of maladaptive drinking (34,70). Moreover, the specific insular activation to affective faces (124) or to appetitive cues (119) may be used as a predictor of alcohol misuse in the future. Interestingly, family history of alcohol dependence was linked to structural abnormalities among healthy first-degree relatives including abnormalities concerning the insula. Namely, individuals with a positive family history of AUD had smaller grey matter volume of the insula compared to those without a family history of AUD (46,65,127).

Animal research confirms the important role of the insula in alcohol-related behaviors (see 138 for a review). For example, studies on rats support the role of the insular cortex in alcohol taking behavior (118), compulsive drinking (37), and context-induced relapse (18).

Another important part of the interoceptive system described by Craig is the ventral medial nucleus of the thalamus. Thalamic shrinkage caused by alcohol misuse was established in both neuropathological (8) and neuroimaging studies (19,115). Despite a significant degree of research investigating alcohol-induced changes in thalamic function and structure, to the best of our knowledge, none described the impact of alcohol use on the nucleus responsible for interoceptive processing. Likewise, there is no research to date concerning the impact of alcohol use on the parasympathetic nucleus of the solitary tract. In turn, there is evidence of alcohol effects on the peripheral components of the interoceptive system for both the sympathetic and parasympathetic paths. Alcohol-related neuropathy was characterized as large-fiber damage caused by nutritional deficiency (especially thiamine), yet Mellion and colleagues (95) described small fiber polyneuropathy in heavy alcohol drinking individuals with normal thiamine status as well. Julian and colleagues (77) have recently published a meta-analysis on neuropathy among individuals with AUD. They established that neuropathy associated with chronic alcohol use is heterogenous and may involve both large and small fibers, while small fiber loss is generally predominant.

To our knowledge, no studies have been conducted so far on the direct effects of alcohol-induced sympathetic afferent damage on interoceptive processing. Recent work has established that vagotomy changes alcohol-related behavior in rats (relapse-like drinking) of a high-alcohol-drinking line (68), suggesting an important role of the peripheral interoceptive system in alcohol use.

Among AUD-related factors, alcohol neurotoxicity is not unique in impacting interoceptive processing at the neurobiological level. There is also evidence that multiple detoxifications following withdrawal during the course of AUD affect the structure and function of the brain. For example, among individuals with AUD experiencing multiple detoxifications, reduction of grey matter volume in cortical brain regions involved in integrating interoceptive signals (e.g., the ventromedial prefrontal cortex and the superior frontal gyrus) was established (45). In addition, neuroimaging studies suggest that repeated detoxifications among participants with AUD were associated with decreased insular connectivity with higher cortical brain regions (e.g., anterior cingulate cortex, orbitofrontal cortex) that are involved in interoceptive processing relative to healthy controls (108). These changes in neural structure and connectivity are associated with emotional impairments, cognitive disabilities, and behavioral deficits that may contribute to relapse (see 44 for a review).

Together these findings indicate that both short- and long-term alcohol use, as well as multiple detoxifications associated with alcohol withdrawal, may be associated with altered interoceptive processing at the neurobiological level, and have consequences that may contribute to alcohol misuse (Fig. 3).

3.3. Interoception deficits in alcohol-related disorders

Considering the important function of the insula in processing the interoceptive signals provided by drug taking and addictive behavior, activation of this structure likely promotes alcohol intake (and craving) in order to repeat previously experienced somatic and emotional relief (103). While some level of alcohol (similar to short-term stress) can be rewarding, repeated alcohol intoxication may initiate neuroadaptations that maintain the allostatic state (83). Findings indicate that a greater discrepancy between interoceptive accuracy and sensibility is associated with symptoms of high arousal (e.g., anxiety; 42), and recent results suggest that high alexithymia may increase this discrepancy (155). In this case, individuals may easily direct their attention to the physical manifestations of emotional arousal instead of the feeling of negative emotion. Although this may serve as a temporary "psychic regulator" to avoid negative emotions, individuals with AUD may choose to use alcohol as an alternative solution to regulate their emotional state. Such conditions may drive alcohol consumption in an effort to regulate one's emotional state and reset the organism to a more natural hedonic/emotional state (81). Further on, changes caused by alcohol consumption during the course of AUD may exacerbate problems with identifying emotions and regulating them.

Despite growing evidence in the role of interoception in the development and maintenance of addictive behaviors and the multidimensional impact of alcohol on the interoceptive system and associated processes, few studies have directly assessed interoceptive abilities in AUD. Unfortunately, different domains of interoception were not precisely defined in these studies, which in the face of later findings, may cause conceptual confusion. Additionally, it should be noted that all of the studies mentioned below assessed only the cardiac modality of interoceptive accuracy (cardioception) in individuals with AUD. To our knowledge, there is currently no published research investigating other modalities of interoception (e.g., gastric or respiratory) in individuals with AUD.[1] It is also important to note procedural variations across reviewed studies using the heartbeat counting task (Schandry Task). Namely, differences include: (1) the number of time intervals used during the test, (2) the duration of these intervals, (3) the heart rate measurement methods, and (4) the instructions given to the participant. These differences may affect the results and their comparability across.

Moreover, research on the original version of the heartbeat counting task shows that it may be influenced by non-interoceptive processes (e.g., heartbeat estimation) and evidence that procedural modifications in the adapted version of the test (i.e., participants asked to avoid estimations) resulted in significant changes (40). Therefore, future studies should consider more stringent standardization of the heartbeat counting task procedure.

Acute alcohol administration impairs interoceptive accuracy (measured through the Schandry Test) in men who drink alcohol (2,87) and alters interoceptive awareness (assessed as the correlation between accuracy on the Schandry Test and confidence of responses) among participants who drink alcohol (87). In addition, in the latter study, researchers established that interoceptive awareness is associated with greater acuity in the perception of alcohol-induced affective and physical changes. On the other hand, Betka and colleagues identified no effect of acute alcohol administration on interoceptive accuracy in non-dependent alcohol drinkers (10). The number of studies on this topic is limited, so the evidence remains inconclusive.

[1] Searching the PubMed database, we found no studies examining interoceptive accuracy using the previously mentioned tests, such as: (1) the Water Load Test or Water Load Test-II, (2) the Respiratory Detection Task, (3) the Respiratory Discrimination Task, and (4) the Soft Touch Task in participants with AUD. However, one study assessed interoceptive processing in adolescents with Substance Use Disorder [SUD] via the Soft Touch Task, documenting interoceptive impairment in comparison with healthy adolescents (96).

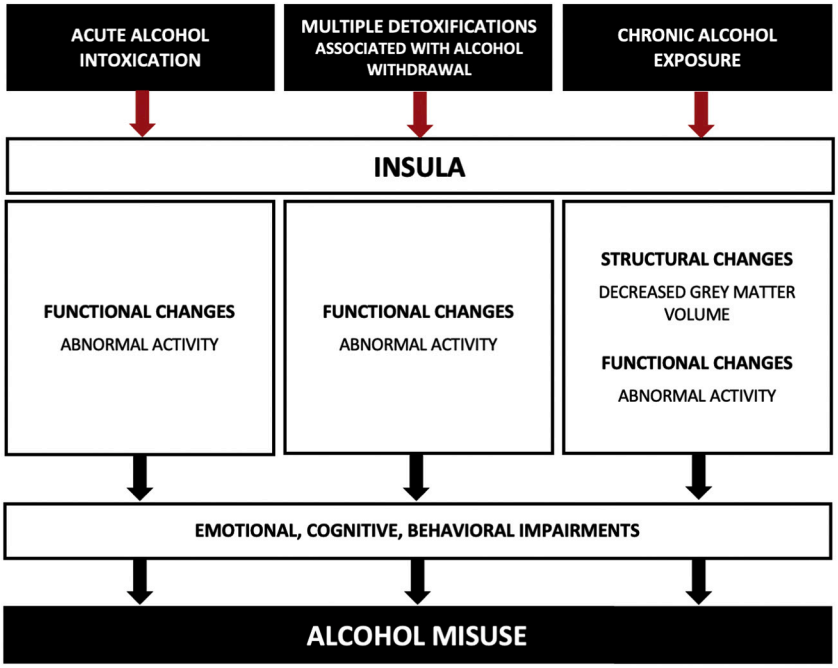

Fig. 3. Acute alcohol intoxication, repeated detoxifications during alcohol withdrawal, and chronic alcohol exposure are associated with structural and functional alterations of the insula (and other cortical levels of the interoceptive system) that may contribute to emotional, cognitive and behavioral impairments. These changes may promote alcohol misuse.

To the best of our knowledge, four studies looked at interoceptive processes among individuals with AUD.[2] Schmidt and colleagues did not find an association between interoceptive accuracy and alcohol behavior (self-reported drinking compulsions/obsessions) in individuals with AUD (122). Yet, they established that interoceptive accuracy was negatively correlated with craving in individuals who had the tendency to decrease negative affect after alcohol use. They also found that deficits in interoception among participants with AUD may increase drinking behavior. Three other studies found that interoceptive accuracy was lower among individuals with AUD in contrast to healthy controls (5,73,133). Additionally, Ateş Çöl and colleagues found that interoceptive accuracy was negatively correlated with alcohol craving (5). In a recent publication, authors observed incongruity between interoceptive accuracy and interoceptive sensibility in individuals with AUD (73). A negative correlation between interoceptive accuracy and difficulties in emotion regulation among individuals with AUD was found. Moreover, an association between high interoceptive sensibility and problems in controlling impulsive behaviors when experiencing negative emotions in this group was established. These observations led the authors to conclude that individuals with AUD that were more interoceptively accurate were more effective in regulating their emotions (74). In addition, the authors observed a negative correlation between interoceptive accuracy and pain sensitivity in AUD individuals (75).

Surprisingly, little research thus far has investigated the different dimensions of interoception among individuals with AUD, despite emerging evidence of the effectiveness of therapy focused on improving the ability to sense signals from the body (mindfulness) in addiction treatment. Interoceptive awareness training was shown to be effective in substance use disorder treatment in women (117). This method has also been associated with better efficiency in substance craving reduction than cognitive behavioral therapy (51). There is some evidence for brain stimulation techniques (e.g., transcranial magnetic stimulation [TMS]) targeting the insula in SUD treatment (69).

4. Conclusions

Neurobiological and psychological findings converge to indicate the significance of interoception in homeostatic processes. Herein, the important role of the insula in interoceptive processing has been acknowledged (114). Accordingly, the allostatic dysregulation brought by repeated alcohol administration could plausibly be perpetuated by altered interoceptive regulatory mechanisms that introduces the disparity between the anticipated and the actual interoceptive state. Moreover, emotional dysregulation, alexithymia, impulsivity and pain processes involved in the sequalae of allostatic dysregulation and largely involved in the development and course of AUD, are related to interoceptive processes and functional integrity of the insula. Given existing work, there is convincing evidence demonstrating that impairment in interoception may be a major contributor to the development and course of AUD. Unfortunately, there are only a few studies that directly evaluate various components of interoception among individuals with AUD, and the methods used to detect objective interoceptive impairments are increasingly criticized. Thus, it should be noted that the associations between interoception and AUD require further research. Moreover, it is important to maintain uniform definitions of the different dimensions of interoception in future research to avoid conceptual confusion. It is also important to unify methods of behavioral interoceptive accuracy testing, which will help facilitate the assessment of future results.

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[2] The following search terms were entered in the PubMed database: ("interoceptive accuracy" OR "interoceptive sensitivity" OR "interoceptive sensibility" OR "interoceptive awareness") AND ("alcohol use disorder" OR "alcohol dependent" OR "alcohol addicted"). The search revealed six studies. The inclusion criteria were the following: (1) only studies on AUD individuals (meeting the ICD-10 criteria for the diagnosis); (2) only studies, which used the Schandry Task to assess interoceptive abilities. One study was rejected due to the method used to assess interoceptive accuracy (i.e., no Schandry Task). Three of them used the same database. One additional study was identified by tracing references from retrieved papers. This search led to the inclusion of four studies.

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Declaration of interests

☒ 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.

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Interoception, alexithymia, and anxiety among individuals with alcohol use disorder

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Background: Interoception (i.e., the ability to recognize bodily signals), alexithymia (i.e., the inability to recognize emotional states) and negative affect (i.e., unpleasant feelings such as anxiety) have been associated with alcohol use disorder (AUD). Previous research suggests that interoception may underlie alexithymia, which in turn may be associated with negative affectivity. However, this remains to be empirically tested. This study investigates whether alexithymia mediates the association between interoception and anxiety and whether this association differs across individuals with AUD and a healthy control (HC) comparison group.

Methods: The AUD group consisted of 99 participants enrolled in an 8-week abstinence-based inpatient treatment program. The HC group included 103 healthy individuals. The heartbeat counting task (HCT) was used to assess interoception (cardiac interoceptive accuracy). The Toronto Alexithymia Scale (TAS-20) was used to assess alexithymia. The Brief Symptom Inventory (BSI) was used to assess anxiety.

Results: The moderated mediation model with interoception as the predictor, alexithymia as the mediator, and negative affect (i.e., state anxiety) as the dependent variable was tested. The analysis showed that the conditional indirect effect of interoception on anxiety via alexithymia was significant for individuals with AUD [$ab = -0.300$, bootstrap 95% CI = (−0.618, −0.088)], as well as for HCs [$ab = -0.088$, bootstrap 95% CI = (−0.195, −0.014)]; however, the conditional indirect effect significantly differed across HCs and individuals with AUD. Namely, the mediated effect was greater among individuals with AUD compared to the HC group.

Conclusion: The results suggests that interoceptive impairment contributes to greater negative affect (i.e., state anxiety) via alexithymia especially for individuals with AUD. Improving emotion recognition via therapeutic methods focused on strengthening interoceptive abilities could improve outcomes for individuals receiving treatment for AUD.

KEYWORDS

interoception, interoceptive accuracy, alexithymia, negative affect, alcohol use disorder

Introduction

Negative affect (i.e., a state of emotional distress associated with unpleasant feelings, such as anxiety, fear, irritability, and sadness) has been shown to be one of the most crucial factors in the development and course of substance use disorder (SUD). Its role in addiction is particularly important according to various theories of negative reinforcement (1–3). These theories emphasize the role that substances play in reinforcing use based on how emotions are experienced. For example, Koob's model of allostatic dysregulation depicts addiction as a multistage process that involves both positive (e.g., pleasant feelings that the substance elicits) and negative (e.g., reducing unpleasant feelings) reinforcement mechanisms (4). Moreover, this model conceptualizes addiction as a disorder that progresses from positive reinforcement to negative reinforcement. According to Hogarth, the negative reinforcement mechanism may be even more relevant to addiction than other mechanisms (such as habit or compulsion) (5). This model indicates that "addiction is primarily driven by an excessive goal-directed drug choice under negative affect." The negative reinforcement theory also applies to individuals with AUD. For example, referring to classical theories of alcohol consumption, which assume that people use alcohol to cope with negative feelings, Wolkowicz and colleagues showed that *the stress-dampening model* may be more important in the early stages of addiction development, while *the tension-reduction model* may be more relevant in heavy-drinking individuals (e.g., individuals with AUD) (6). Among the various phenomena that support negative affectivity as a catalyst for substance use, anxiety is often indicated as a strong motivator for alcohol use (7). Additionally, anxiety is associated with many physical symptoms that involve bodily sensations. Therefore, in this work, we use state anxiety severity as a measure of negative affect.

Negative affectivity among individuals with AUD may be related to impaired mechanisms of emotion regulation in this group. Koob and Volkow highlight alexithymia as one of the key motivational elements that may be a source of unpleasant feelings that uniquely contributes to the cycle of addiction along with dysphoria, irritability and other factors (8). Alexithymia is a clinical construct defined as an inability to recognize and describe emotional states (9). Indeed, it is associated with negative affect among individuals with AUD (10, 11). Prior work supported the use of alcohol as a maladaptive strategy to cope with negative affective states among individuals high in alexithymia (12). Additionally, alexithymia was associated with an earlier age of alcohol use onset, longer duration of problematic drinking, and greater alcohol consumption (13). Moreover, alexithymia also predicted poorer outcomes among individuals with AUD (14). Although the prevalence rate of alexithymia among individuals with AUD is high with estimates between 30 to 67% (15, 16), the factors underlying this overlap remain unclear. In a recent review, Cruise and Becerra (16) conclude that there is convincing evidence supporting alexithymia as an independent risk factor for alcohol-related problems. Further, they point to the growing evidence indicating that alexithymia may be a mechanism through which alcohol-related problems (e.g., emotion dysregulation) lead to AUD. The authors emphasize that it is clinically important to empirically test the nature of the indirect associations between alexithymia and negative affect to inform intervention programming for AUD (16). Importantly, theories are emerging indicating that alexithymia may be related to interoceptive abnormalities (17, 18). Some of these theories even refer to alexithymia as a "general deficit of interoception" (17).

Interoception is the process of bidirectional communication between the brain and internal organs by sensing and interpreting signals arising from within the body and associating them with external stimuli and memory representations to maintain homeostasis (19, 20). Initially, this process was mainly related to biological aspects, but recently its importance in psychological phenomena (e.g., emotion regulation, cognition, self-awareness) has been emphasized (21, 22). Current research recognizes three key domains of interoception: (1) behaviorally measured accuracy or sensitivity, (2) self-reported sensibility, and (3) metacognitive awareness (23). Impairment in interoceptive abilities has been documented in several psychiatric disorders, such as anxiety, depression, autism, and eating disorders (24, 25). There is also significant literature linking disruptions in interoception with addiction [e.g., (26)]. Namely, the notion of embodiment posits that one's emotional state when first experiencing the effects of a drug may exacerbate the difference between the predicted and actual internal state of an individual in the future and, consequently, increase negative affect and promote drug seeking-behavior (27). The association between interoception and AUD is complex [for review see: (28, 29)]. Studies demonstrate decreased interoceptive accuracy in individuals with AUD in comparison to healthy controls (30–32). There is also evidence that interoceptive accuracy is negatively correlated with alcohol craving (30) and difficulties in emotion regulation in individuals with AUD (33).

Deficits in accurately perceiving internal bodily signals may underlie abnormal processing of emotions among individuals with alexithymia. Classical theories of emotion indicate that various emotional states may have their physiological basis in the form of primary changes in the body (34, 35). According to the model of Lane and Schwartz (36), experiencing emotions is a complex process of detailing information, from simple physiological changes in the body to distinguishing individual nuanced emotions. The authors described five levels of emotional experience. The first of these levels, somatic sensation activity, refers to signals coming from the body. At this level, individuals only feel bodily sensations and are unable to describe these sensations in detail. Proper recognition of interoceptive signals is a prerequisite for consciously experiencing, distinguishing, and describing emotions. The authors also emphasize the utility of their theory in understanding alexithymia. In their view, individuals with alexithymia are unable to differentiate between feelings. As a result, individuals high in alexithymia experience arousal (negative affect). This phenomenon may be due to abnormal interoception. More recent work confirms that impaired interoception among individuals with alexithymia may be a source of anxiety (37).

Interestingly, at the neurobiological level, alexithymia is associated with functional impairments in brain regions typically involved in the processing of interoceptive information [e.g., the insula; (38)]. Despite the theoretical basis linking interoception and alexithymia, the results of empirical studies reflecting these associations remain unclear. That is, some studies demonstrate a negative correlation between interoceptive accuracy and alexithymia (18, 39–41), while others show a positive correlation (42, 43) or no correlation (18, 44–46) between the two constructs. In their meta-analysis, Trevisan and colleagues confirmed the association between interoceptive sensibility and alexithymia and showed no association between interoceptive

accuracy and alexithymia (47). However, available research showed that interoceptive accuracy negatively correlates with alexithymia scores among individuals with AUD (32). The study of Betka and colleagues on the association between interoception and alexithymia among social drinkers showed that impaired interoceptive abilities may underlie alexithymia and thus contribute to the use of alcohol as a maladaptive coping strategy (48).

Available data suggests that high alexithymia may be associated with negative affectivity. This in turn may promote alcohol use. A possible underlying mechanism linking alexithymia and negative affectivity may be impaired interoception (17, 18, 48). Thus, we believe that the degree to which impairment in sensing bodily signals is related to negative affectivity may depend on the ability to recognize and describe emotional states. Although the association between interoception, alexithymia, and negative affect has been studied individually, to the best of our knowledge there has been no research that has investigated the combined association between all three factors with an AUD sample. Therefore, the aim of the current study was to assess whether alexithymia mediates the association between interoception and negative affect (i.e., state anxiety) and whether differences exist across individuals meeting criteria for AUD and a healthy control (HC) comparison group using moderated mediation modeling. We hypothesized that alexithymia would mediate the association between interoceptive accuracy and state anxiety. We did not formulate specific hypotheses relating to possible differences across the two groups.

Materials and methods

Participants

The current data comes from an ongoing study examining the emotional and behavioral functioning of individuals with AUD and a HC comparison sample. The study sample consisted of 99 adults (average years of age = 43.4 ± 10.1) who were admitted to an abstinence-based, drug-free, eight-week, inpatient alcohol treatment program incorporating psychoeducation and cognitive-behavioral therapy (CBT). The AUD group consisted of individuals treated in an inpatient setting with severe symptoms of AUD, but without acute withdrawal symptoms. The average duration of abstinence from alcohol was 49.2 ± 45.1 days prior to study enrollment. Study procedures were performed during the first two weeks after treatment admission.

AUD diagnosis using the International Classification of Diseases and Related Health Problems 10th Revision (49) was obtained by a psychiatrist upon treatment admission and then subsequently confirmed via the MINI International Neuropsychiatric Interview (50). Adults with a history of psychosis, current co-occurring mental health disorders requiring medication, current co-occurring substance use disorder other than nicotine, or a clinically significant cognitive deficit (< 25 on the Mini-Mental State Examination) (51) were not eligible.

HCs included 103 adults (average years of age = 40.4 ± 8.4) that met with a general practitioner for a yearly physical examination or for medical advice [see (52) for additional description of the study sample]. In HCs, study procedures were performed prior to the routine visit to their primary care physician. Adults endorsing harmful alcohol use as assessed via the Alcohol Use Disorders Identification Test [AUDIT; (53)] were not eligible. A large portion of the sample encompasses White men (AUD 87%, HC 76%) consistent with the demography of patients admitted in substance use treatment programs in Poland. When comparing groups on demographic factors, the HC sample was significantly younger [$F(1, 200) = 5.05$, $p = 0.03$] and more likely to be female [χ^2 (1, 202) = 4.1, $p = 0.04$] compared to the AUD sample. Accordingly, age and biological sex were added as covariates in subsequent analyses.

The current study adopted ethical principles outlined in the Declaration of Helsinki in 1964. Moreover, the Bioethics Committee of the institution where the study took place approved the study procedures.

Measures

Sociodemographic information

Sociodemographic characteristics (e.g., age, biological sex, education) were queried with a self-report survey.

Alcohol use factors

The Short Inventory of Problems (54) was used to assess the maximum amount of alcohol consumed during consecutive heavy drinking periods, the number of consecutive days of heavy drinking, and the length of abstinence from alcohol use prior to the assessment through the use of a semi-structured interview. A modified version of the Substance Abuse Outcomes Module (55) was used to determine the duration of problematic alcohol use among individuals with AUD based on self-reported age of drinking problem onset.

Negative affect

The anxiety score from the Brief Symptoms Inventory [BSIanx; (56)] was used to assess negative affect severity. The BSI has been used as a valid indicator of negative affect and psychological distress (12). It was shown that negative affectivity may be more related to anxiety compared to depression (57). Cronbach's α for the total BSI score was 0.97.

Alexithymia

The Polish version of the self-reported Toronto Alexithymia Scale [TAS-20; (58)] was used to assess alexithymia. Three subscale scores were assessed: (1) difficulty describing feelings (e.g., "It is difficult for me to find the right words for my feelings"; (2) difficulty identifying feelings (e.g., "I am often confused about what emotion I am feeling"; and (3) externally oriented thinking (e.g., "I prefer to analyze problems rather than describe them"; Cronbach's αs = 0.60–0.84 across TAS subscales and total score). For the current study, a total score comprised of the sum of these subscales was analyzed.

Interoception

The modified version of Schandry's heartbeat counting task [HCT; (59)] involves asking study participants to silently count their heartbeats across trials of different lengths (i.e., 25 s, 35 s and 45 s). The participants were told not to use helping strategies, such as assessing their pulse on their hand or neck. Actual heartbeats were recorded simultaneously using a standard electrocardiogram with 12 electrodes attached to the chest and limbs. The following

TABLE 1 Interoceptive accuracy, alexithymia, and anxiety severity in individuals with alcohol use disorder (AUD) and healthy controls (HC).

	AUD[a] (*N* = 109*)	HC[a] (*N* = 145*)	*t*[b]	*p*
Interoceptive accuracy	0.72(0.08)	0.49(0.29)	7.74	< 0.001
TAS(total)	45.98(10.76)	56.51(11.21)	−7.53	< 0.001
TAS(ddf)	12.78(3.82)	15.01(3.86)	−4.59	< 0.001
TAS(dif)	15.08(4.49)	21.41(5.69)	−9.58	< 0.001
BSI(anx)	0.24(0.34)	0.88(0.76)	−8.21	< 0.001

Interoceptive accuracy – calculated using the following formula: $1/3\sum(1-(|\text{actual heartbeats}-\text{reported heartbeats}|)/\text{actual heartbeats})$.
TAStotal – Toronto Alexithymia Scale total score; TASddf - Toronto Alexithymia Scale Difficulty Describing Feelings; TASdif - Toronto Alexithymia Scale Difficulty Identifying Feelings; BSIanx – Brief Symptom Inventory anxiety severity.
[a]Values are means and standard deviations.
[b]*t*-Student test was applied to measure the mean score difference between individuals with alcohol use disorder and healthy controls.* for Schandry Test AUD N = 104 and HC *N* = 106.

TABLE 2 Correlations between interoceptive accuracy, alexithymia, and anxiety severity in individuals with alcohol use disorder (AUD) and healthy controls (HC).

		Interoceptive accuracy	TAS(total)	TAS(ddf)	TAS(dif)	BSI(anx)
Interoceptive accuracy	r (N)		−0.24** (202)	−0.18* (202)	−0.22** (202)	−0.15* (204)
TAS(total)	r (N)	−0.24** (202)		0.79** (254)	0.88** (254)	0.39** (253)
TAS(ddf)	r (N)	−0.18* (202)	0.79** (254)		0.65** (254)	0.34** (253)
TAS(dif)	r (N)	−0.22** (202)	0.88** (254)	0.65** (254)		0.47** (253)
BSI(anx)	r (N)	−0.15* (204)	0.39** (253)	0.34** (253)	0.47** (253)	

* Pearson two-sided correlation at the level < 0.05.
** Pearson two-sided correlation at the level < 0.01.
Interoceptive accuracy – calculated using the following formula: $1/3\sum(1-(|\text{actual heartbeats}-\text{reported heartbeats}|)/\text{actual heartbeats})$.
TAStotal – Toronto Alexithymia Scale total score; TASddf - Toronto Alexithymia Scale Difficulty Describing Feelings; TASdif - Toronto Alexithymia Scale Difficulty Identifying Feelings; BSIanx – Brief Symptom Inventory anxiety severity.

formula was used to calculate interoceptive accuracy: $1/3\sum(1-(|\text{actual heartbeats}-\text{reported heartbeats}|)/\text{actual heartbeats})$. A score of 1 equals a perfect match between self-reported and actual heartbeats. This method of measuring and calculating an *interoceptive accuracy index* is widely used in the field [e.g., (31, 39, 41, 60–62)].

Data analysis

Means, standard deviations in interoceptive accuracy, alexithymia and anxiety severity in individuals with AUD and HCs are presented in Table 1. Correlations between interoceptive accuracy, alexithymia and anxiety severity in individuals with AUD and HCs are presented in Table 2. Hayes' (63) PROCESS macro for SPSS to estimate moderated mediation with bootstrapping (5,000 resamples with replacement) was used to test AUD status as a moderator in the role of alexithymia as a mediator linking interoception and anxiety severity (see Figure 1 for a conceptual model). Namely, alexithymia was included as a mediator in the link between interoception on anxiety, with AUD status moderating the second association (i.e., the link between alexithymia and anxiety) while controlling for age and biological sex. Simple slope analyses were used to determine the nature of significant interactions. This entails estimating subsequent multiple regressions to assess the exact value of the moderator where the predictor (i.e., the mediator) has an effect on the dependent variable. Non-standardized coefficient values are presented. In PROCESS, an index of moderated mediation with a value outside of 0 is representative of an indirect effect that is conditional on the moderator (i.e., support for moderated mediation).

Results

The moderated mediation model (63) with interoception (*HCT*) as a predictor, alexithymia (*TAS-20*) as mediator, and anxiety (*BSIanx*) as the dependent variable was tested (see Figure 2 for non-standardized coefficients). The model explained 9% of the variance in alexithymia ($R^2 = 0.09$; $F[3,198] = 6.26$; $p < 0.01$) and 38% of the variance in anxiety ($R^2 = 0.38$; $F[6,195] = 20.10$; $p < 0.01$). There was support for a significant two-way interaction between alexithymia and AUD status [$\Delta R^2 = 0.02$; $F(1,195) = 5.93$; $p = 0.02$] on anxiety. As depicted in Figure 3, findings indicate that the simple slope for the regression of anxiety on alexithymia was statistically significant for individuals with AUD [$b = 0.023$; 95% CI = (0.014, 0.032); $p < 0.001$], but not for HCs ($b = 0.007$; 95% CI = [−0.003, 0.016]; $p = 0.161$). That is, alexithymia was positively associated with anxiety, but only among individuals with AUD. Nevertheless, the conditional indirect effect of interoception on anxiety via alexithymia was significant for individuals with AUD [$ab = -0.300$, bootstrap 95% CI = (−0.618, −0.088)], as well as HCs ($ab = -0.088$, bootstrap 95% CI = [−0.195, −0.014]). However, the conditional indirect effect across individuals with AUD and HCs differed significantly (index of moderated mediation: ab_{AUD} - $ab_{HC} = -0.211$, bootstrap 95% CI = [−0.497, −0.028]. That is, the role of alexithymia as a potential mediator in the association between interoception and anxiety was more pronounced for individuals with

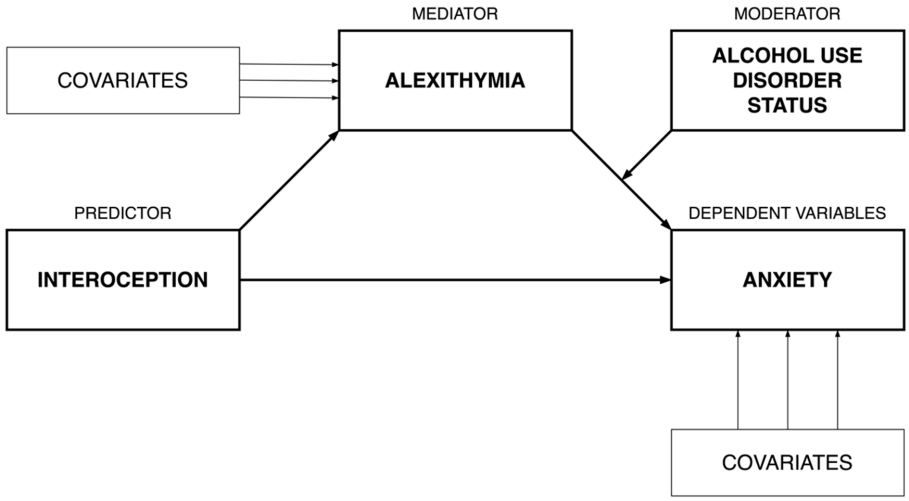

FIGURE 1
Conceptual diagram for moderated mediation model.

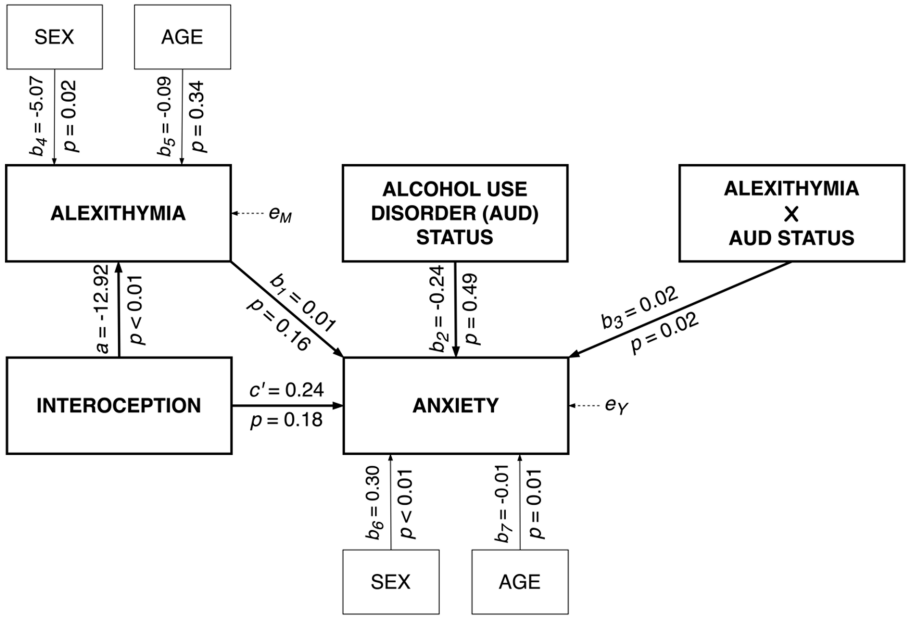

FIGURE 2
Moderated mediation model for anxiety.

AUD compared to HCs and this may be due to a stronger link between alexithymia and anxiety among those with an AUD.

Discussion

The main goal of this study was to investigate the interconnections between interoception, alexithymia, and negative affect (i.e., state anxiety) among individuals with AUD and a healthy control comparison group. To the best of our knowledge, this represents the first study testing whether alexithymia mediates the association between interoception (i.e., behaviorally measured cardiac interoceptive accuracy) and negative affect (i.e., current anxiety symptom severity), and if this association differs across groups (i.e., AUD vs. HC) using moderated mediation. The results show that across individuals with AUD and HCs, lower interoceptive accuracy is associated with greater alexithymia. In addition, AUD status was found to moderate the association between alexithymia and current anxiety symptom severity. Namely, alexithymia fully mediated the association between interoception and state anxiety in the same direction for both study groups, but the effect was significantly larger within the AUD sample.

It is commonly believed that alexithymia and interoception are related to each other. This is largely based on three factors: 1)

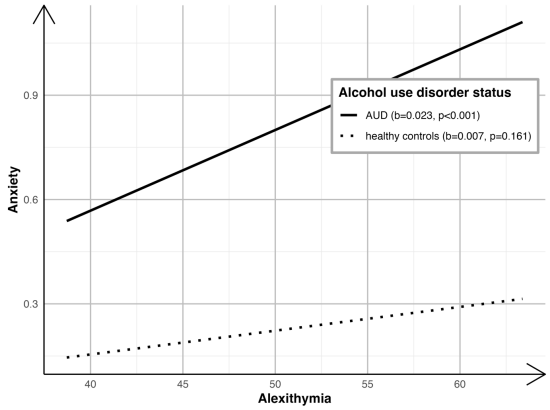

FIGURE 3
Alexithymia on anxiety by AUD status.

according to some traditional theories of emotion, perception of bodily signals plays an important role in emotional processing (34); 2) alexithymia is present in a broad range of psychiatric disorders associated with decreased interoceptive abilities (64), and 3) certain brain regions engaged in interoceptive processing [e.g., the insula; (65)] are also associated with alexithymia (66). Modern theories even describe alexithymia as "a general deficit of interoception" (17). Nevertheless, despite the theoretical background, empirical research in this field is contradictory and methodologically inconsistent due to difficulties in conceptualizing and measuring interoception (47). For example, the authors of a recent meta-analysis found an association between self-reported interoception and alexithymia. Yet, the association between interoceptive accuracy and problems with identifying emotions (a component of alexithymia) was nonsignificant (47). In contrast, our study found evidence of a significant negative association between interoceptive accuracy and alexithymia across individuals with AUD and HCs. Individuals with impairments in recognizing interoceptive signals (i.e., heartbeat) reported greater alexithymia. Importantly, as stated earlier, it may be inappropriate to compare the results of studies utilizing subjective measures of interoception [see (47)] and those utilizing objective measures, as in the current study. Our findings are in line with earlier research, which confirmed a negative correlation between interoceptive accuracy and alexithymia in non-clinical samples (18, 39–41). However, as mentioned previously, there is some prior work supporting a positive correlation [e.g., (42)] or no correlation [e.g., (45)] between interoceptive accuracy and alexithymia. Thus, our results may supplement conflicting findings across the extant literature. Scarpazza and colleagues (61) put forward two hypotheses to explain mixed findings across the literature. The first suggests that individuals with alexithymia display impaired interoceptive abilities due to difficulties identifying and interpreting bodily changes on a cognitive level, which affects their subjective emotional experience. The other states that individuals with alexithymia may present heightened interoceptive accuracy because they experience emotions in a more "physical" way (42). These hypotheses are not mutually exclusive, as alexithymia may be the result of disturbed emotional processing at different levels of emotional awareness (36).

The association between interoception and alexithymia among individuals with AUD is understudied. This is surprising given the theoretical basis for such connections (26). Namely, deficits in the body's sensing ability that contribute to difficulties in recognizing emotional states, which is characteristic of individuals with AUD (26), link alexithymia to interoception. Alexithymia was also found to moderate the association between subjective interoception and alcohol intake in individuals that binge drink (48). Moreover, neuroimaging studies showed numerous similarities between interoception, alexithymia, and neurobiological correlates of AUD [for review see (28)]. Consistent with prior work (32), we found that individuals with AUD demonstrating impaired interoceptive accuracy had greater alexithymia. However, Sönmez and colleagues (32) only found a negative correlation between interoceptive accuracy and a specific feature of alexithymia: difficulty identifying feelings in a sample of individuals with AUD. The authors of the latter study also indicated similar associations among individuals with varying substance use disorders, including heroin and synthetic cannabinoids (32). Our results may therefore expand upon the sparse empirical data to support an association between alexithymia, interoception, and problematic alcohol use.

As expected, our findings showed that high levels of alexithymia were associated with greater negative affect (i.e., current anxiety symptom severity) across individuals with AUD and a HC comparison group, but only significant in the former group. Prior work has supported associations between alexithymia and negative affect in HC samples (67), as well as in individuals with AUD (68). There is evidence that alexithymia is associated with anxiety. Research shows that difficulty recognizing emotions is related to both state anxiety and trait anxiety. Interestingly, among the different dimensions of alexithymia, two that are related to state anxiety are the inability to identify and describe feelings and to distinguish between feelings and bodily sensations (69, 70). Our findings indicate that alexithymia was significantly lower in the HC sample compared to individuals with AUD. It is plausible that only high levels of alexithymia may lead to increased levels of anxiety, while lower levels of alexithymia characterizing HCs may not be clinically relevant.

The main finding in this study that alexithymia mediated the association between interoception (interoceptive accuracy) and state anxiety may contribute to a greater understanding of the association between alexithymia, interoception, and alcohol misuse. According to several theories, bodily signals are important in the conscious experience of emotion. James and Lange (34) postulated that experiencing emotions was related to primary bodily changes. Damasio (35) later named the neural representations of these changes "somatic markers" that trigger emotions and drive behavior. More recent theories of embodiment claim that the mental representations of bodily changes formed during the original emotional experience are then reused when re-exposed to the emotional stimulus (71, 72). According to these theories, proper recognition of interoceptive signals is a prerequisite for consciously experiencing, distinguishing, and describing emotions. Thus, individuals high in alexithymia may experience anxiety due to abnormal interoception. Our results are consistent with this hypothesis and contribute to the expanding literature on the interoceptive basis of alexithymia (17, 18, 48).

Based on the above considerations, we believe that individuals with lower interoceptive abilities and associated difficulties in describing their emotional states are more likely to experience anxiety (i.e., unpleasant arousal). Alcohol may be used by these individuals as a coping strategy. This can lead to the development of addiction via

negative reinforcement mechanisms. Interestingly, in individuals with AUD, as negative reinforcement increases, AUD severity also increases (73). This mechanism may be related to the negative effect of alcohol on interoceptive abilities and thus on abilities in describing one's emotional states, which may in turn increase the level of aversive states, such as anxiety, fueling the vicious circle of addiction.

The results of our research can contribute to improving treatment programs for AUD and informing alcohol use prevention programs. Given that high alexithymia in individuals with AUD is associated with poorer treatment outcomes (74), improving emotion recognition may be an important therapeutic goal. A way to improve alexithymia may be to enhance interoceptive abilities. Previous data show that therapeutic approaches that target improving body awareness can increase one's ability to recognize emotional states (75). More specifically, the work of Bornemann and Singer suggests that improvements in interoception affects the ability to recognize one's own emotions, rather than vice versa (46).

This current study has some limitations. The main limitation of this study is the use of HCT to measure interoception. Despite the frequent use of this test in research on interoceptive accuracy, methodological weaknesses have been raised (18, 45, 76, 77). Namely, heartbeats may be perceived to some extent exteroceptively (77). The knowledge of the average heart rate may affect the results obtained using HCT (76). In their paper, Zamariola and colleagues summarized the main problems with HCT pointing out the following: 1) under-reporting of heartbeats; 2) low correlation between total actual heartbeats and total recorded heartbeats; 3) negative correlation between interoceptive accuracy and heart rate; and 4) differences in interoceptive accuracy scores across HCT trials (45). However, Ainley and colleagues commented on Zamariola's paper and refuted most of the criticisms, they confirmed that HCT leads to underreporting of heartbeats, but that this limitation requires further empirical testing (78). Nevertheless, according to other research, the results of HCT correspond well with other interoceptive tasks (79). Recently, a study indicated that HCT can be a reliable test in assessing interoceptive accuracy (80). In the absence of alternative methods to study this phenomenon, we decided to use HCT, which will further allow us to compare our results with those obtained in prior work. However, we note the need for future research aimed at identifying additional methods to test interoceptive accuracy.

With regard to other limitations, the current study included participants from an inpatient treatment program for AUD with a severe course of the disorder and negative consequences of drinking. Thus, findings may not generalize to less severe cases of AUD. In addition, compared to HCs, individuals in the AUD group were older and more likely to be male. Although, both sex and age were used as control variables in all analyses, our results cannot be generalized to woman and/or individuals from other racial/ethnic groups. Older age in individuals with AUD may have also affected the results, as damage to the nervous system caused by long-term alcohol consumption may impair interoceptive accuracy. Moreover, due to the small number of women in the study, we cannot determine possible biological sex differences. We did not collect data on participants' body weight in this study. This is a limitation as body weight may affect interoceptive accuracy (81).

In conclusion, the results of the current study show that alexithymia mediates the association between interoceptive impairment and negative affect. Moreover, the indirect effect was found to be significantly greater among individuals with AUD compared to HCs. Clinically, the current findings indicate that improving emotion recognition via therapeutic methods focused on strengthening interoceptive abilities could have utility for individuals receiving treatment for AUD. Future work empirically testing the value in bolstering interoception to enhance emotion recognition to buffer against negative affect among individuals with AUD should be conducted.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Bioethics Committee of Medical University of Warsaw. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

PW, AJ, ET, PK, HS, JZ, MR, and MK contributed to the conception and design of the work. PW, AJ, JZ, MR, and MK contributed to the acquisition of data. MK, ET, AJ, PK, and HS assisted with the analysis and interpretation of data. PW and MK managed the literature research and wrote the first draft of manuscript. AJ, ET, PK, HS, JZ, and MR revised and provided substantial input on the manuscript. All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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The synergistic effect between interoceptive accuracy and alcohol use disorder status on pain sensitivity

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HIGHLIGHTS

- Individuals with alcohol use disorder (AUD) and healthy control were recruited.
- Interoceptive accuracy (IAc) and pain sensitivity were assessed.
- IAc negatively correlated with pain sensitivity in individuals with AUD.
- AUD status moderated the association between IAc and pain sensitivity.

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ABSTRACT

Background: Interoceptive accuracy and pain sensitivity are both risk factors in the development of alcohol use disorder (AUD). However, the synergistic association between these two factors has not been investigated in an AUD sample. Therefore, the aim of the current study was to investigate whether the association between interoceptive accuracy and sensitivity to pain differed across AUD status.

Methods: The study group included 165 individuals diagnosed with AUD (88.1% men) and 110 healthy controls (HCs; 74.5% men). Interoceptive accuracy was assessed with the Schandry Task. The Pain Sensitivity Questionnaire was utilized to measure sensitivity to pain. Anxiety, biological sex, and age were included as covariates in a model examining the role of AUD status as a moderator in the association between interoceptive accuracy and pain sensitivity.

Results: A significant interaction was found between interoceptive accuracy and AUD status ($b = -4.580$, 95% CI = $[-8.137, -1.022]$, $p = 0.012$, $\Delta R^2 = 0.032$). Findings indicate that interoceptive accuracy was negatively associated with pain sensitivity among individuals with AUD, while there was a trend for an opposite association among healthy controls.

Conclusion: We hypothesize that persistent alcohol drinking may contribute to disruption of the normative association between interoception and pain. Future studies should be conducted to develop knowledge on this association and to investigate its possible therapeutic significance and implications.

1. Introduction

Chronic pain is a common condition among individuals with alcohol use disorder (AUD) (Jakubczyk et al., 2015; Katon, Egan, & Miller, 1985). Moreover, experiencing physical pain may contribute to the development and more severe course of AUD (Maleki, Tahaney, Thompson, & Oscar-Berman, 2019). Witkiewitz and colleagues (2015) found that greater physical pain predicted higher rates of heavy drinking, as well as drinking lapses, during and following AUD treatment (Witkiewitz et al., 2015). Hyperalgesia (i.e., increased sensitivity to pain) is a common symptom of alcohol withdrawal (Gatch, 2009), while persistent heavy alcohol use likely causes health problems that

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are commonly associated with pain (e.g., polyneuropathy, hepatitis, gastritis) (Rehm et al., 2017). A reduction of physical pain also reduces risk of relapse in individuals with AUD (Jakubczyk et al., 2016). Thus, connections between heavy alcohol use and physical pain have been established in prior work.

Recently, AUD has been conceptualized as a "chronic pain disorder" (Egli, Koob, & Edwards, 2012) due to significant overlap in neurobiological correlates and genetic links across these conditions. Important predictors in the development and severe course of AUD (e.g., impulsivity, anxiety and depressive symptoms, sleep problems) were all shown to be associated with more severe physical pain (Jakubczyk et al., 2015). There is evidence suggesting common underpinnings of physical pain and AUD that go beyond the analgesic effect of ethanol. Reward, emotional, and nociceptive systems are thought to represent overlapping circuitry across alcohol anticipation and withdrawal, as well as pain in animal models (Robins, Heinricher, & Ryabinin, 2019). Yet, the underlying biological mechanisms linking physical pain and AUD in humans remain elusive. A recent review (Edwards, Vendruscolo, Gilpin, Wojnar, & Witkiewitz, 2020) concludes that there is a critical need to conduct more research on clinical populations with AUD, especially without comorbid opioid dependence, to inform possible connections linking pain and AUD. Importantly, research shows that the association between pain and alcohol drinking may vary across clinical and non-clinical populations (Brennan, Schutte, & Moos, 2005). Namely, Yeung and colleagues (Yeung, Lee, McDowell, Sher, & Gizer, 2020) observed that among individuals without AUD, alcohol consumption was associated with lower pain interference at follow-up. However, among men with greater AUD symptom severity, the opposite association was observed, with greater alcohol consumption being significantly related to greater pain severity (Yeung et al., 2020). Therefore, work investigating factors impacting pain processing and how this may differ across individuals with and without AUD may be particularly informative.

Interoception (i.e., the way one perceives signals from the body) may represent a factor that could contribute in part to both AUD and pain processing. In terms of AUD, interoception may lead to problematic substance use by influencing the "embodied" (felt as internal state of the body) experience of substance use or withdrawal. Prior work has consistently demonstrated that lower levels of embodied perception of alcohol intoxication predict higher risk for AUD (Schuckit et al., 2009). Recent conceptualizations specify distinct phenomena to describe how one perceives interoceptive stimuli: interoceptive accuracy (also known as interoceptive sensitivity: precision in perceiving real internal processes measured behaviorally, e.g., heartbeat perception) and sensibility (the tendency to focus on internal body sensations). Studies indicate that individuals with AUD are characterized by lower interoceptive accuracy and higher sensibility in comparison to healthy controls (Jakubczyk et al., 2019b). Moreover, drinking alcohol was shown to decrease interoceptive accuracy in non-AUD participants (Abrams et al., 2018), which may characterize a vicious cycle leading to AUD development.

From a therapeutic perspective, treatments focused on enhancing interoception awareness skills, such as mindfulness-based interventions, were shown to be effective in treating women with a substance use disorder (Price, Thompson, Crowell, & Pike, 2019; Price et al., 2018). Importantly, interoceptive accuracy has been linked to better emotion regulation, which is considered an important protective factor in AUD. Low interoceptive accuracy was associated with deficits in emotion regulation and the association between interoceptive sensibility and emotion regulation was moderated by AUD status (Jakubczyk et al., 2019a). Thus, similar to work conducted on pain conditions, examining interoception and its relation to pain perception across AUD and non-AUD samples will likely have clinical utility.

In terms of pain, prior work indicates that it can be conceptualized as an interoceptive stimulus similar to other internal stimuli (Craig, 2002). It follows that interoceptive sensitivity would be positively correlated with pain sensitivity. Indeed, Pollatos and colleagues showed that in healthy individuals greater interoceptive accuracy was significantly associated with enhanced pain sensitivity, including lower pain thresholds and decreased pain tolerance (Pollatos, Fustos, & Critchley, 2012). Yet, a recent review demonstrated that chronic pain conditions (e.g., fibromyalgia, somatization disorder) are characterized by deficits in interoceptive accuracy and that interoceptive accuracy negatively correlates with pain severity (Di Lernia, Serino, & Riva, 2016). Similarly, high pain sensitivity was significantly correlated with high interoceptive accuracy in healthy controls, while among a group of patients with somatoform disorder, an opposite direction was reported (Weiss, Sack, Henningsen, & Pollatos, 2014). Work conducted on patients with non-cardiac chest pain also demonstrated that those reporting high levels of chest pain were less accurate at heartbeat perception (i.e., lower interoceptive accuracy). Taken together, this work indicates that the association between pain and interoceptive accuracy among populations experiencing high levels of pain may differ compared to healthy individuals.

To our knowledge, prior work has not examined associations between physical pain and interoception among individuals with AUD. Given studies emphasizing the importance of both pain and interoception in the development of AUD, a greater understanding of synergistic associations across these factors could have significant clinical utility. The aim of the current study was to investigate whether the association between interoceptive accuracy and sensitivity to pain differed across AUD status. It was hypothesized that among individuals with AUD (conceptualized as a chronic pain disorder) interoceptive accuracy will be negatively associated with pain sensitivity. In contrast, it was hypothesized that interoceptive accuracy will be positively associated with pain sensitivity among healthy controls.

2. Material and methods

2.1. Participants and procedures

2.1.1. Individuals with AUD

This study was comprised of 165 adults admitted to an eight-week, drug-free, abstinence-based, inpatient alcohol treatment program. Given the overrepresentation of men in substance use treatment programs in Poland, a majority of the sample was comprised of White men (88.1%). Participants were 44 ± 11.2 years of age, on average. In terms of drinking characteristics, participants reported: 1) first experiencing drinking problems during early adulthood (25.7 ± 9.6 years of age); 2) that the duration of the last drinking period before starting the treatment was approximately 70 days (69.5 ± 196.6; range = 1–1460); and 3) the duration of alcohol abstinence prior to completing the study procedures was 49.2 ± 45.1 days. Thus, participants represent individuals with severe symptoms of AUD, but the absence of acute withdrawal symptomatology. Study procedures were performed during the first two weeks after treatment admission.

AUD diagnosis was derived using the International Classification of Diseases and Related Health Problems 10th Revision (WHO, 1992) upon admission to the treatment center and was later confirmed through the MINI International Neuropsychiatric Interview (Sheehan, Lecrubier, Sheehan, Amorim, Janavs, Weiller, Hergueta, Baker, & Dunbar, 1998). Individuals were excluded if they met criteria for a clinically significant cognitive deficit (< 25 on the Mini-Mental State Examination) (Folstein, Folstein, & McHugh, 1975) or met criteria for any of the following: a history of psychosis, co-occurring psychiatric disorders requiring current medication, co-occurrence of opioid dependence, or the presence of acute alcohol withdrawal symptoms.

2.1.2. Healthy controls

A healthy control (HC) group was included to investigate whether associations between interoceptive accuracy and pain sensitivity differs across AUD status. This group (n = 110; 74.5% men) was comprised of

individuals meeting with a primary care physician for medical advice or a yearly physical examination. In addition to exclusion criteria for individuals with AUD, HCs were excluded if they endorsed harmful alcohol use based on the Alcohol Use Disorders Identification Test (Babor & Higgins-Biddle, 2000). Participants were 40.6 ± 8.1 years of age. When comparing the two groups across demographic characteristics, HCs were significantly younger ($F[1,266] = 7.65$, $p = 0.006$) and less likely to be male (x^2 [1, 269] = 8.2, $p = 0.004$). Thus, age and biological sex were included as covariates in all analyses.

This study was conducted in accordance with the ethical principles described in the Declaration of Helsinki in 1964 and received approval from the Bioethics Committee of the institution where the study took place.

2.2. Measures

2.2.1. Psychiatric comorbidity

Comorbidity was assessed with the Polish version of the MINI International Neuropsychiatric Interview (Folstein et al., 1975; Masiak & Przychoda, 1998). The Polish version of the Brief Symptom Inventory (BSI) (Derogatis & Melisaratos, 1983) was utilized to assess anxiety symptoms, which have been associated with experiencing pain (Gureje et al., 2008). Thus, anxiety was also included as a covariate.

2.2.2. Pain sensitivity

Pain sensitivity was assessed with the Polish version of the Pain Sensitivity Questionnaire (Ruscheweyh, Marziniak, Stumpenhorst, Reinholz, & Knecht, 2009; Latka et al., 2019). This is a 17-item measure reflecting self-reported subjective pain sensitivity in everyday situations (e.g., "Imagine you bump your elbow on the edge of a table"). Three out of the 17 items describe nonpainful situations. Therefore, the PSQ score was presented as a mean of the 14 pain-related items (Ruscheweyh et al., 2009). Participants are asked to rate how painful each situation would be on a scale of 1 (not at all painful) to 10 (most severe pain imaginable). The Cronbach's α for this scale was 0.92.

2.2.3. Current experience of pain

A visual analogue scale (VAS) for pain assessment was adopted. Participants were asked to add a tick mark on a 10 cm horizontal line ranging from "no pain at all" to the "worst pain imaginable" reflecting their current experience of physical pain. This was used as a supplementary tool to confirm that individuals with AUD report more overall severe pain in comparison to HCs.

2.2.4. Interoceptive accuracy

The mental tracking task developed by Schandry (Schandry, 1981) was administered by instructing participants to silently count their heartbeats in trials of different lengths (25 s, 35 s and 45 s). Interoceptive accuracy was calculated using the following formula: 1/3 ∈(1–(|actual heartbeats – reported heartbeats|)/actual heartbeats). Perfect correspondence between the reported and actual heartbeats is equal to one. The Schandry Test is the most widely used test to assess interoceptive accuracy and prior work indicates that it is a reliable indicator of interoceptive accuracy (Zimprich, Nusser, & Pollatos, 2018; Ainley, Tsakiris, Pollatos, Schulz, & Herbert, 2018) and that it corresponds well with other interoceptive tasks (Herbert, Muth, Pollatos, & Herbert, 2012). Importantly, previous studies examining interoceptive accuracy among AUD samples also utilize the Schandry Test (Jakubczyk et al., 2019b; Abrams et al., 2018; Jakubczyk et al., 2019a).

The heartbeat perception test was available for 86 individuals with AUD (52%) and 104 (94%) HCs. There were no significant differences in psychopathological characteristics or measures assessing pain between those individuals with and without available Schandry test data.

2.2.5. Interoceptive sensibility

The Private Body Consciousness subscale (PBCS) (Miller, Murphy, & Buss, 1981) from the Body Consciousness Questionnaire consists of five items related to the tendency to focus on internal body sensations. Specifically, it assesses awareness of hunger, body temperature, dry mouth/throat, heart beating and internal bodily tensions (e.g., "I am sensitive to internal body tensions"). Higher scores indicate greater interoceptive sensibility. Cronbach's α for this scale was 0.71. Although no specific hypotheses for interoceptive sensibility were made *a priori*, this measure was included to determine whether other aspects of interoception relate to pain across AUD status.

2.3. Data analysis

Correlations between pain sensitivity, anxiety, and both measures of interoception were conducted to examine associations across relevant constructs. One-way analysis of variance (ANOVA) tests were also conducted comparing individuals with and without AUD on pain sensitivity, current experience of physical pain, and severity of anxiety. Interoceptive accuracy and sensibility among groups has already been reported elsewhere (Jakubczyk et al., 2019a).

To test AUD status as a potential moderator of the effect of interoceptive accuracy on pain sensitivity, Preacher and Hayes' (2008) PROCESS macro for moderation analysis with bootstrapping (5000resampleswithreplacement) in SPSS was used. Fig. 1 illustrates the conceptual diagram for the model. Simple slope analyses reflecting a "pick-a-point" approach were conducted to probe significant interactions (Hayes, 2018). Non-standardized coefficients are reported throughout the paper.

3. Results

Within the AUD group, 39.4% of individuals rated current pain as 0, while 71.8% of HCs rated current pain as 0. Among individuals with AUD, level of anxiety and age were positively associated with pain sensitivity, whereas in HCs only interoceptive sensibility was positively correlated with pain sensitivity (see Table 1).

As expected, individuals with AUD were characterized by significantly higher pain sensitivity (PSQ score), more severe pain intensity (VAS), and greater anxiety, as compared to HCs (see Table 2). Pain sensitivity in the AUD group was not associated with duration of abstinence.

The model (N = 184) estimating the synergistic effect between AUD status and interoceptive accuracy explained 12% of the variance in pain sensitivity ($R^2 = 0.120$; $F[6, 177] = 4.053$; $p < 0.001$; see Fig. 2).

A significant interaction was found between interoceptive accuracy and AUD status ($b = -4.580$, 95% CI = [−8.137, −1.022],

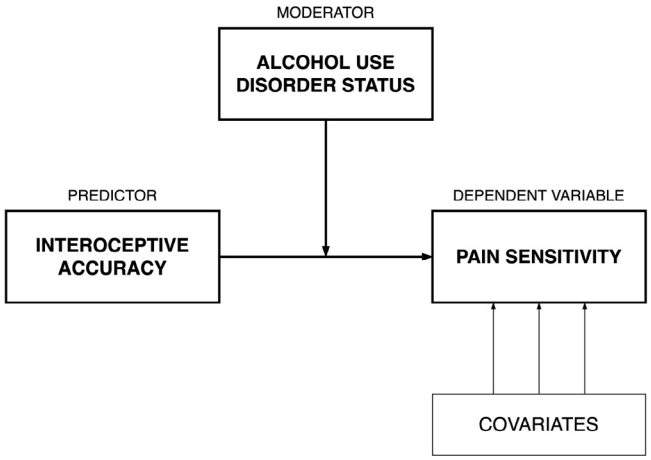

Fig. 1. Conceptual diagram for the association between interoceptive accuracy and alcohol use disorder status on pain sensitivity accounting for covariates (anxiety symptoms, sex, age).

Table 1
Pain, interoception, and anxiety correlations across individuals with alcohol use disorder and health controls (*Note.* AUD = alcohol use disorder, HC = healthy control, BSI = Brief Symptom Inventory– anxiety symptoms, PSQ = Pain Sensitivity Questionnaire, PBCS = Private Body Consciousness Subscale).

		Pain Sensitivity (PSQ)	
		AUD	HC
Age	*r*	**0.164**	−0.085
	p	**0.049**	0.380
Interoceptive accuracy	*r*	**−0.237**	0.158
	p	**0.034**	0.109
Interoceptive sensibility (PBCS)	*r*	0.080	**0.234**
	p	0.348	**0.015**
Anxiety (BSI)	*r*	**0.189**	0.156
	p	**0.023**	0.103
Duration of abstinence	*r*	−0.09	(–)
	p	0.309	

Table 2
Differences in demographic, pain, and anxiety characteristics across individuals with alcohol use disorder and healthy controls. (*Note.* SD = standard deviation, AUD = alcohol use disorder, HC = healthy control, BSI = Brief Symptom Inventory – anxiety symptoms, PSQ – Pain Sensitivity Questionnaire, VAS – Visual Analogue Scale, PBCS = Private Body Consciousness subscale).

	AUD Group (mean ± SD)	HC Group (mean ± SD)	*p*
Biological sex [%men]	88.1 (N = 159)	74.5 (N = 110)	0.004
Age	44.0 ± 11.2 (N = 158)	40.6 ± 8.1 (N = 110)	0.006
Pain sensitivity (PSQ)	3.96 ± 1.62 (N = 144)	3.35 ± 1.31 (N = 110)	0.002
Current pain severity (VAS)	1.02 ± 1.64 (N = 142)	0.46 ± 1.16 (N = 110)	0.003
Anxiety (BSI)	0.9 ± 0.8 (N = 145)	0.2 ± 0.3 (N = 110)	< 0.005
Interoceptive sensibility (PBCS)	17.3 ± 4.1 (N = 141)	14.8 ± 4.1 (N = 107)	< 0.0005
Interoceptive accuracy (Schandry score)	0.61 ± 0.16 (N = 86)	0.72 ± 0.08 (N = 104)	< 0.0005

$p = 0.012$, $\Delta R^2 = 0.032$). When probing the interaction, findings indicate that the simple slope for the regression of pain sensitivity on interoceptive accuracy was statistically significant for individuals with AUD ($b = -2.180$; 95% CI = [−4.002, −0.357]; $p = 0.019$), but not for HCs ($b = 0.122.60$; 95% CI = [−0.648, 5.448]; $p = 0.122$; see Fig. 3). That is, interoceptive accuracy was negatively associated with pain sensitivity among those with AUD.

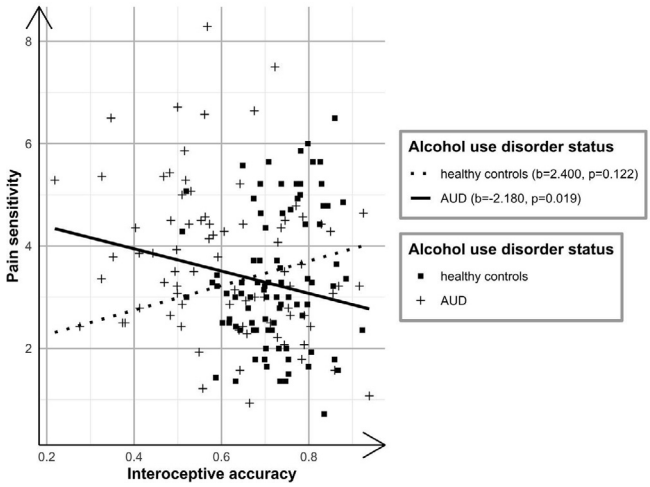

Fig. 3. Interoceptive accuracy on pain sensitivity by alcohol use disorder status.

4. Discussion

Consistent with hypotheses, findings indicate that among individuals with AUD interoceptive accuracy was negatively correlated with pain sensitivity. Moreover, AUD status significantly moderated the association between interoceptive accuracy and pain sensitivity. Although the association between interoceptive accuracy and pain sensitivity was not statistically significant among healthy controls, there was a visible trend suggesting that this association may be in the opposite direction (i.e., better interceptive accuracy is associated with greater pain sensitivity; see Fig. 3). This trending effect is consistent with prior work conducted on healthy individuals supporting a link between interoceptive accuracy and pain sensitivity (Pollatos et al., 2012; Weiss et al., 2014). The current study is among the first to investigate differences that may exist in the association between interoceptive accuracy and pain sensitivity across a clinical group of individuals with AUD compared to healthy participants.

The current findings are consistent with prior work on interoception, pain, and the nuances that emerge across clinical and non-clinical samples. Weiss and colleagues observed that greater pain sensitivity was significantly associated with greater interoceptive accuracy among healthy controls, whereas the opposite pattern emerged among patients with somatoform disorder (Weiss et al., 2014). Similarly, studies on populations with chronic pain reveal that these patients are

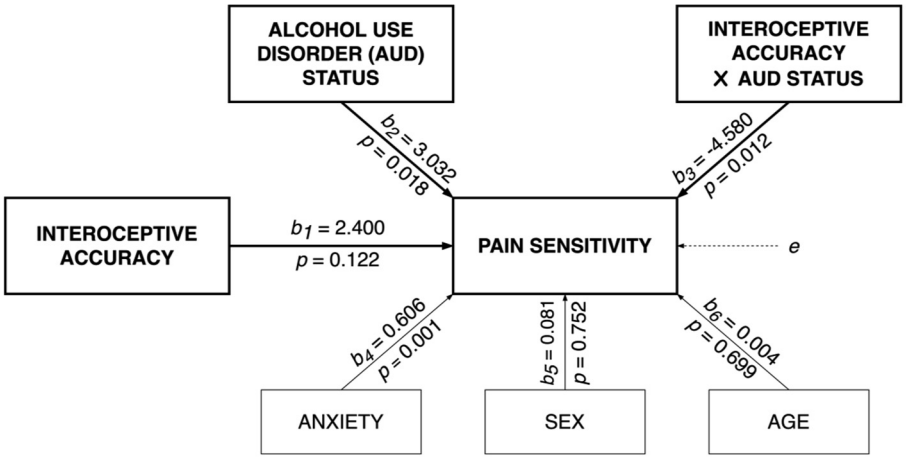

Fig. 2. Effects of interoceptive accuracy and AUD status on pain sensitivity. *Note.* Coefficients are not standardized.

characterized by significant deficits in interoceptive accuracy and that interoceptive accuracy is negatively correlated with pain severity (Di Lernia et al., 2016). Interestingly, somatic disorders related to pain (e.g., migraine, fibromyalgia, somatoform disorder) that are associated with low interoceptive accuracy are also linked to comorbid negative affectivity or emotion dysregulation (Trucharte et al., 2020; Gerhart et al., 2018; Louter et al., 2015), which are key risk factors in the development of AUD (Koob, 2015).

Prior work indicates that normative processes connecting pain sensitivity and interoceptive accuracy may be disrupted within individuals with AUD given two possible factors. The first is chronicity of pain. Chronic pain was shown to be associated with negative emotional states, like sleep problems, depressive symptoms or emotion dysregulation (Gureje et al., 2008), which can increase pain sensitivity (Reynolds, Carpenter, & Tragesser, 2018) and at the same time decrease IAc (Jakubczyk et al., 2019a). Importantly, the PSQ was shown to be significantly correlated with experimental pain intensity ratings (Ruscheweyh et al., 2009). Thus, pain sensitivity may be interpreted as a reliable measure of general, not acute (e.g., as measured by the VAS) pain intensity. Unfortunately, detailed data regarding the duration of pain was not available within our sample. Yet, given the fact that the AUD group was characterized by a long history and high severity of drinking problems (which likely lead to somatic diseases), the pain experienced by this group may have been chronic rather than acute in nature. An important future direction involves directly investigating the possible distinction between acute and chronic pain in relation to interoception and emotion regulation among those with AUD. This differentiation is important, as acute pain constitutes a protective factor (enables fast and effective removal or avoidance of harmful stimuli), while chronic pain represents a condition where nociception no longer acts as a useful, adaptive process. Instead chronic pain becomes associated with negative emotional states (Gureje et al., 2008), which can escalate the experience of pain. Notably, alcohol is commonly used to alleviate pain (almost 70% of individuals with AUD in our sample confirmed drinking alcohol for analgesic purposes). Therefore, persistent use of alcohol to reduce pain or in prophylaxis against pain, may be conceptually comparable to chronic pain.

The second factor which is likely to disrupt normative processes in the interoception-pain connection is anxiety. Although the broader literature supports a link between increased cardiac interoceptive sensitivity (accuracy) and anxiety-related phenotypes (Domschke, Stevens, Pfleiderer, & Gerlach, 2010), greater interoceptive accuracy might not be specific to health anxiety, but rather associated with other factors shared among all anxiety disorders (Krautwurst, Gerlach, & Witthoft, 2016). Prior work examining individuals that are characterized by anxiety symptoms related to one's own somatic state demonstrate a strong association between high anxiety and low interoceptive accuracy (Krautwurst, Gerlach, Gomille, Hiller, & Witthoft, 2014). In this case, somatic sensations are rather the result of the overactivity of the central nervous system, rather than the real perception of internal stimuli (Pang et al., 2019).

Populations with AUD are also characterized by a tendency to focus on internal somatic states, high levels of anxiety (Jakubczyk et al., 2019b), as well as low interoceptive accuracy (Jakubczyk et al., 2019b). Thus, it may be that when experiencing pain conditions, individuals with AUD who are characterized by low interoceptive accuracy may not be capable of correctly identifying the nature of pain; therefore, anxiety may increase over time. Thus, a negative association between interoceptive accuracy and pain sensitivity may result from possible alcohol-related damage in interoceptive peripheral pathways, which overlap with those responsible for pain perception (Craig, 2003). In general, the knowledge on associations between interoception, anxiety and alcohol drinking is scarce, and these relationships should be examined thoroughly in future studies to confirm the hypotheses stated above.

The current findings support trends that most healthy controls have adequate interoceptive accuracy (Pollatos et al., 2012; Weiss et al., 2014). That is, most healthy individuals who are better at recognizing internal/somatic sensations (i.e., higher interoceptive accuracy) are also more sensitive to potentially harmful stimuli (i.e., higher pain sensitivity). In this case, healthy individuals are more likely to feel pain earlier if a damaging stimulus appears and employ both emotional and somatic (interoception) mechanisms to react adaptively to this stimulus. Our results add to the larger literature by showing that the association between pain sensitivity and interoceptive accuracy may have an opposite pattern among individuals with AUD, which resembles the associations observed previously in chronic pain and somatoform disorders (Di Lernia et al., 2016; Weiss et al., 2014). This association may have particular utility given prior work indicating that interoception is critical in emotional regulation. For example, Craig (Craig, 2002) indicated that interoception is best understood as a physiological condition of the entire body, not just the internal organs. It follows that interoception has a significant impact on how one experiences emotions (Craig, 2002). Thus, greater interoceptive accuracy might constitute a general positive precondition for effective emotional self-regulation (Craig, 2002).

If greater interoceptive accuracy (linked with better emotion regulation) is associated with lower pain sensitivity, then among individuals with AUD, higher interoceptive (emotional) functions could become available when the pain sensitivity is low. Importantly, our AUD sample was characterized by significantly higher pain sensitivity in comparison to HCs. Therefore, it's likely that individuals with AUD may use alcohol in order to decrease pain sensitivity and (as a consequence of the reverse pattern of pain-IAc connection) increase interoceptive accuracy, achieving subjective (somatic and emotional) well-being.

In non-AUD subjects alcohol remains a well-known analgesic substance, it does decrease pain sensitivity, but at the same time it disrupts emotion regulation, and decreases interoceptive accuracy (Abrams et al., 2018). Also, the need to decrease pain sensitivity in HCs may not be a priority, as they are characterized by significantly lower pain sensitivity in comparison to individuals with AUD. In general, higher pain sensitivity might be adaptive only in the case of acute stress, such as pain, when the damaging factor can be immediately relieved; yet it becomes maladaptive as higher pain sensitivity transitions into a chronic experience as observed among individuals with AUD. The opposite pattern in the interoception-pain connection among individuals with AUD may be viewed as an adjustment to the chronic use of ethanol for the purpose of pain relief. The direction of effects in the current study is in line with the theory of the "Dark side of Addictions" formulated by Koob (Koob, 2017), which outlines the significance of "*recruitment of brain stress systems that drive aversive states.*" Namely, persistent alcohol use may expose the "dark side of pain" in addictions, whereby disruptions in the interoception-pain connection lead to perseveration of harmful states as opposed to relieving them.

It is important to note that the current study design does not allow for any causal inferences. The association between interoceptive accuracy and pain sensitivity is likely bidirectional. Interoception seems to be a broader phenomenon than pain, which constitutes one possible interoceptive stimulus among others. Thus, our statistical models reflected interoception as a possible catalyst of changes in pain perception. However, the opposite direction is also probable. Here, it can be speculated that when pain is experienced, its emotional component engages central nervous system areas responsible for interoception. Hence, resources may be taken up by pain processing, leaving them unavailable for executive interoception (and plausibly, emotion regulation). Neurobiological studies confirm that pain is processed via peripheral interoceptive pathways. Yet, the central neural circuits involved in the processing of pain stimuli also overlap with those responsible for interoception (Paulus & Stewart, 2014; Ong, Stohler, & Herr, 2019). Specifically, the insula is crucial for translating interoceptive/emotional/pain stimuli into activation of the cognitive control network to implement goal-directed behavior. It has been found that

alcohol affects crucial elements of the interoceptive system. Acute alcohol administration was shown to disrupt functional connectivity between the right anterior insular cortex and the anterior cingulate cortex in healthy participants, which resulted in a calming effect (Gorka, Phan, & Childs, 2018) and impaired decision-making (Sherman, Rosenbaum, & Smith, 2019). Chronic alcohol misuse has also been associated with structural changes of the insula (e.g., grey matter volume reduction) (Yang, Tian, & Zhang, 2016). Functional abnormalities involving increased insular activity (Olbrich et al., 2006; Strosche, Zhang, & Kirsch, 2020) in response to alcohol-related stimuli and its decreased activation when involved in cognitive processes (Li, Luo, Yan, Bergquist, & Sinha, 2009) were observed. In addition, there is evidence that alcohol negatively affects peripheral parts of the interoceptive system by damaging small diameter A and C fibers, which are also involved in pain processing (Julian, Glascow, Syeed, & Zis, 2019).

In general, there is convincing evidence that reward, emotional, control, and nociceptive systems represent overlapping circuitry across alcohol anticipation and withdrawal, as well as pain (Maleki et al., 2019; Robins et al., 2019; Edwards et al., 2020). Our results contribute just another, but possibly important element, namely interoception, to the comprehensive work connecting human emotional and somatic processes (Craig, 2002). A greater understanding of the associations between pain, interoception, and emotions may help identify possible targets for clinical interventions. Plausibly, AUD treatment programs could benefit from working on harmonization of pain and interoceptive processing. Specifically, perhaps it could be valuable to enhance interoception awareness skills and simultaneously address coping with pain strategies (Price et al., 2019; Ehde, Dillworth, & Turner, 2014). This could likely affect emotion regulation and behavioral control. To test this hypothesis, future work should directly investigate whether associations between emotion dysregulation and pain sensitivity differ across populations with and without AUD symptoms. Also, it would be useful to investigate directly in a lab setting, how administration of ethanol influences IAc in individuals with AUD.

Our study has important limitations that should be noted. The project employed a cross-sectional design and only participants from an inpatient treatment program for AUD were recruited. These are individuals with a severe course of AUD. Therefore, impaired interoception and pain sensitivity might have been influenced by heavy alcohol use and our results may not generalize to less severe cases of AUD. Individuals with AUD were significantly more likely to be male and older in comparison to healthy controls. Although age and sex were used as control variables in all analyses, the older age of individuals with AUD may have influenced the results, as age is associated with higher pain sensitivity among individuals with AUD due to emerging polyneuropathy. The study employed only self-report assessments of pain sensitivity and did not assess chronicity of pain. Future work should also utilize behavioral measures of pain threshold and account for the duration of experienced pain.

5. Conclusions

Results indicate that the association between interoceptive accuracy and pain sensitivity may be moderated by AUD status. Yet, future work should seek to gain a deeper understanding of this association and to investigate its possible therapeutic significance and implications.

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CRediT authorship contribution statement

Andrzej Jakubczyk: Conceptualization, Methodology, Writing - original draft, Supervision. **Paweł Wiśniewski:** Resources, Writing - review & editing. **Elisa M. Trucco:** Conceptualization, Formal analysis, Writing - review & editing. **Paweł Kobyliński:** Formal analysis, Visualization, Writing - review & editing. **Justyna Zaorska:** Investigation, Data curation, Writing - review & editing. **Jakub Skrzeszewski:** Investigation, Data curation, Writing - review & editing. **Hubert Suszek:** Software, Methodology, Writing - review & editing. **Marcin Wojnar:** Project administration, Writing - review & editing. **Maciej Kopera:** Conceptualization, Methodology, Writing - original draft, Supervision.

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.

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Podsumowanie

Artykuły składające się na tę rozprawę uzupełniają wiedzę na temat znaczenia interocepcji w mechanizmach rozwoju i podtrzymywania uzależnienia od alkoholu. Dokonana w nich ocena zależności pomiędzy interocepcją a aleksytymią, bólem i negatywną emocjonalnością w grupie osób z rozpoznaniem UA wydaje się być podejściem dotychczas nieobecnym w literaturze.

W wyniku przeprowadzonych analiz potwierdzono, że osoby z rozpoznaniem UA cechują się gorszą dokładnością interoceptywną niż osoby zdrowe. Podobne wyniki prezentowano we wcześniejszych opracowaniach, ale badania te prowadzone były na niewielkich grupach badanych (23-25). Obserwowane różnice wydają się zrozumiałe, jeżeli weźmie się pod uwagę negatywny wpływ alkoholu na istotne elementy układu interoceptywnego – strukturę i funkcję kory wyspowej czy wolne zakończenia nerwowe autonomicznego układu nerwowego zaangażowane w odbieranie sygnałów generowanych wewnątrz ciała. Należy jednak przypomnieć, że występujące pierwotne zaburzenia interocepcji również mogą sprzyjać rozwojowi UA i trudno jednoznacznie ustalić przyczynowość w tej zależności. Wyniki uzyskane w przekrojowym badaniu na to nie pozwalają.

W dalszej kolejności ustalono, że osoby, które charakteryzują się gorszą dokładnością interoceptywną (gorzej rozpoznają sygnały napływające z ciała) gorzej rozpoznają własne stany emocjonalne (cechują się wyższą aleksytymią). Zależność tę obserwowano zarówno w grupie osób z UA, jak też osób zdrowych. Dotychczasowe badania co prawda potwierdzały podobne relacje pomiędzy zmiennymi u osób z UA (25), ale dawały sprzeczne rezultaty w odniesieniu do osób zdrowych (32). Dostępne w literaturze dane dają teoretyczne podstawy do powiązania aleksytymii z interocepcją. W badaniach neurobiologicznych potwierdzono znaczenie kory wyspowej, będącej ważnym ośrodkowym centrum przetwarzania sygnałów interoceptywnych, w rozpoznawaniu własnych stanów emocjonalnych (31). Dodatkowo, niektóre z teorii emocji przypisują duże znaczenie sygnałom napływającym z wnętrza ciała w procesie generowania i rozpoznawania emocji. Wobec niejednoznacznych danych empirycznych, niniejsze wyniki mogą stanowić ważne uzupełnienie aktualnej wiedzy.

Dodatkowo stwierdzono również, że większe nasilenie aleksytymii wiąże się z większym nasileniem negatywnej emocjonalności (lęku). Zależność tę obserwowano w obu badanych grupach, ale tylko wśród uzależnionych od alkoholu była ona istotna statystycznie. Wydaje się, że wysoki poziom aleksytymii u osób z UA może prowadzić do zwiększonego nasilenia lęku, podczas gdy niższe poziomy aleksytymii charakteryzujące osoby zdrowe mogą

nie mieć znaczenia klinicznego. We wcześniejszych badaniach wskazywano już na związki aleksytymii z lękiem (48). Co ciekawe, powiązano lęk z trudnościami w rozróżnianiu między uczuciami a doznaniami cielesnymi, które to trudności stanowią jeden z wymiarów aleksytymii (49, 50).

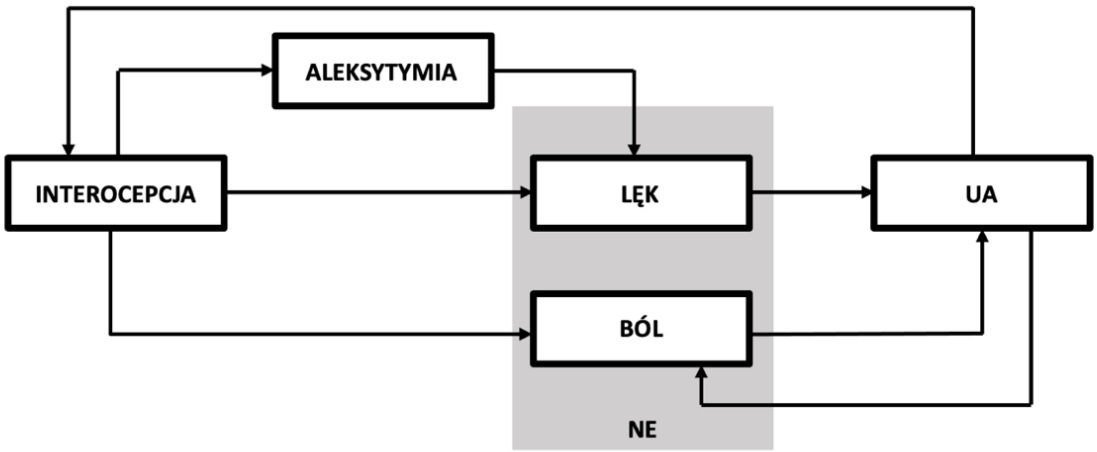
W wyniku przeprowadzonych analiz ustalono, że u osób z rozpoznaniem UA gorsza dokładność interoceptywna była związana z wyższym nasileniem lęku. Zależności pomiędzy interocepcją a lękiem były szeroko omawiane w dotychczasowych opracowaniach. Jest to zrozumiałe, ponieważ lęk związany jest z wieloma objawami dotyczącymi zmian w ciele. Wiele zaburzeń lękowych powiązano z nieprawidłową interocepcją. Dotychczasowe badania związków między różnymi wymiarami lęku a poszczególnymi domenami interocepcji dawały jednak niejednoznaczne wyniki. W jednej z ostatnich metaanaliz nie stwierdzono związku między dokładnością interoceptywną a lękiem u zdrowych osób (42). Dostępne w literaturze dane sugerowały jednak, że zależność ta może być istotna u osób uzależnionych od alkoholu (25). Wyniki tego badania dały podobne rezultaty.

W badaniach składających się na tę rozprawę ustalono również, że aleksytymia pełni rolę mediatora związku między interocepcją (dokładnością interoceptywną) a negatywną emocjonalnością (lękiem). Zależność tę obserwowano zarówno w grupie osób z rozpoznaniem UA, jak i grupie kontrolnej osób zdrowych. Efekt był istotnie silniejszy w tej pierwszej. Co ważne, dotychczas nie dokonywano podobnych analiz. Według teorii emocji, które wskazują na istotną rolę sygnałów napływających z wnętrza ciała w procesie generowania emocji te wyniki wydają się zrozumiałe. Zaburzenia w zakresie dokładności interoceptywnej mogą uniemożliwić prawidłowe rozpoznanie emocji i przyczyniać się do powstawania nieprzyjemnych stanów takich jak chociażby lęk.

W przeprowadzonych badaniach wykazano, że osoby z rozpoznaniem UA charakteryzują się istotnie większą wrażliwością na ból i większym nasileniem bólu. Wynik ten jest zgodny z danymi dostępnymi w literaturze (36). W grupie osób z UA stwierdzono ujemną korelację między dokładnością interoceptywną i wrażliwością na ból – osoby, które lepiej przetwarzały sygnały napływające z ciała, charakteryzowały się mniejszą wrażliwością na ból. W grupie kontrolnej osób zdrowych obserwowano odwrotny trend, ale zależność nie była istotna statystycznie. Wyniki te są zgodne z zakładanymi hipotezami i spójne z dostępnymi danymi. Podobne zależności obserwowano dotychczas niezależnie u osób z rozpoznaniem UA oraz zdrowych, ale nie dokonywano analiz porównawczych. Osoby zdrowe o wysokich zdolnościach interoceptywnych były opisywane jako bardziej wrażliwe na ból (47), a osoby doświadczające przewlekłego bólu (może to dotyczyć dużego odsetka uzależnionych od

alkoholu) miały gorsze zdolności interoceptywne (37). Co ważne, powiązano również przewlekły ból z negatywną emocjonalnością, która dodatkowo może nasilać samo doświadczanie bólu.

Używanie alkoholu może stanowić nieadaptacyjną strategię radzenia sobie z nieprzyjemnymi stanami emocjonalnymi takimi, jak na przykład lęk czy ból. Trudności w rozpoznawaniu własnych stanów emocjonalnych mogą być związane z lękiem. U podłoża aleksytymii może z kolei leżeć nieprawidłowe odczytywanie sygnałów napływających z ciała. Według teorii negatywnego wzmacniania mechanizm ten może przyczyniać się do rozwoju uzależnienia. Wraz z rozwojem UA dokładność interoceptywna może się pogarszać, a wraz z nią wzrastać wrażliwość na ból i lęk. Ten złożony mechanizm może przyczyniać się do podtrzymywania uzależnienia, a jego formę graficzną przedstawiono na Ryc. 1.



Ryc. 1. Zależności między interocepcją, aleksytymią, lękiem i bólem a uzależnieniem od alkoholu. (UA – uzależnienie od alkoholu, NE – negatywna emocjonalność)

Analizowane w niniejszym opracowaniu zależności stanowią ważne uzupełnienie wiedzy w zakresie znaczenia interocepcji w przebiegu uzależnienia od alkoholu i mogą mieć istotne znaczenie kliniczne. Pozwalają na wyodrębnienie nowych celów terapeutycznych w leczeniu UA. Wpływ na rozpoznawanie własnych emocji poprzez poprawę zdolności interoceptywnych może przyczynić się do poprawy, dotychczas niezadowalających, wyników leczenia. Dodatkowe znaczenie może mieć uzupełnienie programów terapeutycznych o strategie radzenia sobie z przewlekłym bólem. Wyniki nielicznych badań oceniających skuteczność terapii ukierunkowanych na ciało (np. mindfulness) w populacji osób z UA przynoszą obiecujące rezultaty.

Uzyskane wyniki potwierdzają, że badanie zdolności interoceptywnych w populacji osób z rozpoznaniem UA może mieć duże znaczenie w kontekście poznania mechanizmów uzależnienia oraz istotne implikacje kliniczne. Nadal niewiele jest prac poświęconych ocenie różnych domen interocepcji wśród osób uzależnionych od alkoholu. Ciekawe mogą okazać się badania odnoszące się do innych wymiarów interocepcji (np. oddechowego czy gastrycznego) w tej grupie osób. Wreszcie interesujące byłyby analizy związków między interocepcją a innymi czynnikami ryzyka UA. Poszerzanie wiedzy w tym zakresie wydaje się zasadne i potrzebne.

Ograniczenia

Włączone do niniejszej rozprawy analizy mają ograniczenia, o których należy wspomnieć. Osoby uzależnione od alkoholu zrekrutowane do badania to w zdecydowanej większości mężczyźni charakteryzujący się ciężkim przebiegiem uzależnienia, co uniemożliwia określenie różnic międzypłciowych i uogólnienie wyników na populację pacjentów o mniejszym nasileniu uzależnienia. Do oceny dokładności interoceptywnej wykorzystano Test Zliczania Uderzeń Serca (*Heartbeat Counting Task – HCT*), którego wartość metodologiczna jest coraz częściej kwestionowana. Pomimo zarzutów metoda ta nadal stosowana jest w badaniach nad interocepcją a jej wyniki korelują z innymi miarami interocepcji (51). Z coraz większą stanowczością podkreśla się jednak konieczność poszukiwania alternatywnych metod oceny zjawiska (8). Bardziej szczegółowy opis ograniczeń czytelnik znajdzie jeszcze w poszczególnych artykułach.

Wnioski

1. Osoby z rozpoznaniem UA charakteryzują się istotnie gorszą dokładnością interoceptywną niż osoby zdrowe.
2. (A) U osób z rozpoznaniem UA gorsza dokładność interoceptywna jest istotnie związana z wyższą aleksytymią i większą negatywną emocjonalnością (lękiem). (B) Aleksytymia jest mediatorem zależności między dokładnością interoceptywną a negatywną emocjonalnością (lękiem).
3. U osób z rozpoznaniem UA gorsza dokładność interoceptywna jest istotnie związana z większą wrażliwością na ból, podczas gdy u osób zdrowych obserwowana jest odwrotna zależność.

Komisja Bioetyczna
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KB/.258...../2016

Komisja Bioetyczna przy Warszawskim Uniwersytecie Medycznym

w dniu 13 grudnia 2016 r. po zapoznaniu się z wnioskiem:

dr hab. n. med. Andrzej Jakubczyk
Katedra I Klinika Psychiatryczna
ul. Nowowiejska 27, 00-665 Warszawa

dotyczącym: wyrażenia opinii w sprawie badania pt „ Ból i świadomość interoceptywna u osób zdrowych oraz uzależnionych od alkoholu.

wyraża następującą
opinię

- stwierdza, że jest ono dopuszczalne i zgodne z zasadami naukowo-etycznymi*.
- ~~stwierdza, że jest ono niedopuszczalne i niezgodne z zasadami naukowo-etycznymi.*~~

Uwagi Komisji – *verte*

Komisja działa na podstawie art.29 ustawy z dnia 5.12.1996r. o zawodzie lekarza /Dz.U.nr 28/97 poz.152 wraz z późn.zm./, zarządzenia MZiOS z dn.11.05.1999r. w sprawie szczegółowych zasad powoływania i finansowania oraz trybu działania komisji bioetycznych /Dz.U.nr 47 poz.480/, Ustawy prawo farmaceutyczne z dnia 6 września 2001r. (Dz.U.Nr 126, poz. 1381 z późn. zm.) oraz Zarządzenie nr 56/2007 z dnia 15 października 2007r. w sprawie działania Komisji Bioetycznej przy Warszawskim Uniwersytecie Medycznym /Regulamin Komisji Bioetycznej przy Warszawskim Uniwersytecie Medycznym/.
Komisja działa zgodnie z zasadami GCP .
W załączeniu: skład komisji oraz lista obecności

Przewodniczący Komisji Bioetycznej

Prof. dr hab. n. med. Zbigniew Wierzbicki

*niepotrzebne skreślić

Komisja wyraża pozytywną opinię w sprawie przeprowadzenia wnioskowanych badań- na warunkach określonych we wniosku oraz dodatkowo zastrzegając:
1/ obowiązek przedstawienia Komisji:

- wszystkich zmian w protokole mających wpływ na przebieg oraz ocenę badania,
- wszystkich przypadków zdarzeń niepożądanych,
- zawiadomienia o przyczynach przedwczesnego zakończenia badania,
- sprawozdania w toku przeprowadzonych badań-za sześć miesięcy,
- raportu końcowego.

strona podpisowa do uchwały Komisji Bioetycznej przy Warszawskim Uniwersytecie Medycznym nr KB/258 z dnia 13 grudnia 2016r.

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2. Prof. dr hab. Barbara GAJKOWSKA .....
3. Prof. dr hab. med. Jadwiga KOMENDER .....
4. Prof. dr hab. med. Bożenna WOCIAL .....
5. Prof. nadzw. dr hab. med. Andrzej KAŃSKI .....
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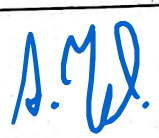
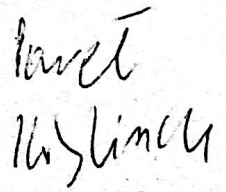
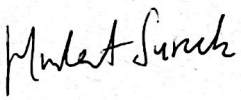
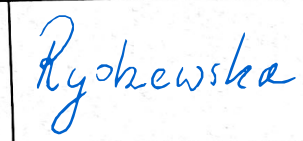
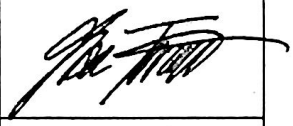
13. Prof. dr hab. Joanna GÓRNICKA-KALINOWSKA .....
14. Alicja JAWORSKA .....
15. Ksiądz Władysław GRĘDOWSKI .....

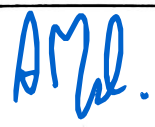
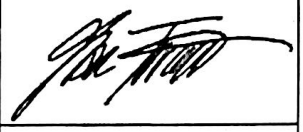
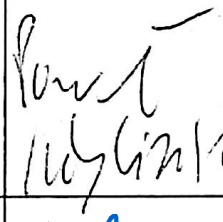
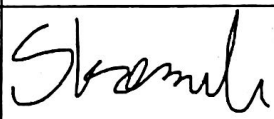
Oświadczenia wszystkich współautorów publikacji określające indywidualny wkład każdego z nich w ich powstanie

Interoception, alexithymia, and anxiety among individuals with alcohol use disorder.			
Imię i nazwisko współautora	Wkład	Wkład procentowy	Podpis
Paweł Wiśniewski	Opracowanie założeń pracy, gromadzenie danych, przegląd literatury, napisanie pierwszej wersji pracy	80%	
Andrzej Jakubczyk	Opracowanie założeń pracy, gromadzenie danych, analiza i interpretacja danych, sprawdzanie i edycja manuskryptu	4%	
Elisa M. Trucco	Opracowanie założeń pracy, sprawdzanie merytoryczne pracy, analiza i interpretacja danych, sprawdzanie i edycja manuskryptu	4%	
Paweł Kobyliński	Opracowanie założeń pracy, analiza i interpretacja danych, sprawdzanie i edycja manuskryptu	4%	
Hubert Suszek	Opracowanie założeń pracy, sprawdzanie merytoryczne pracy, analiza i interpretacja danych, sprawdzanie i edycja manuskryptu	2%	
Justyna Zaorska	Opracowanie założeń pracy, gromadzenie danych, sprawdzanie i edycja manuskryptu	2%	
Małgorzata Rydzewska	Opracowanie założeń pracy, gromadzenie danych, sprawdzanie i edycja manuskryptu	2%	
Maciej Kopera	Opracowanie założeń pracy, gromadzenie danych, analiza i interpretacja danych, przegląd literatury, napisanie pierwszej wersji pracy	2%	

Oświadczenia wszystkich współautorów publikacji określające indywidualny wkład każdego z nich w ich powstanie

Alcohol use and interoception - A narrative review.			
Imię i nazwisko współautora	Wkład	Wkład procentowy	Podpis
Paweł Wiśniewski	Przegląd literatury, napisanie pierwszej wersji pracy	80%	
Pierre Maurage	Sprawdzanie merytoryczne pracy, edycja manuskryptu	4%	
Andrzej Jakubczyk	Sprawdzanie merytoryczne pracy, edycja manuskryptu	4%	
Elisa M. Trucco	Sprawdzanie merytoryczne pracy, edycja manuskryptu	4%	
Hubert Suszek	Sprawdzanie merytoryczne pracy, edycja manuskryptu	4%	
Maciej Kopera	Sprawdzanie merytoryczne pracy, edycja manuskryptu	4%	

Oświadczenia wszystkich współautorów publikacji określające indywidualny wkład każdego z nich w ich powstanie

The synergistic effect between interoceptive accuracy and alcohol use disorder status on pain sensitivity.			
Imię i nazwisko współautora	Wkład	Wkład procentowy	Podpis
Andrzej Jakubczyk	Opracowanie założeń pracy, metodologia, pisanie pierwszej wersji pracy, nadzór	45%	
Paweł Wiśniewski	Sprawdzanie i edycja manuskryptu	40%	
Elisa M. Trucco	Opracowanie założeń pracy, analiza i interpretacja danych, sprawdzanie i edycja manuskryptu	3%	
Paweł Kobyliński	Analiza i interpretacja danych, prezentacja danych, sprawdzanie i edycja manuskryptu	3%	
Justyna Zaorska	Gromadzenie danych, sprawdzanie i edycja manuskryptu	3%	
Jakub Skrzeszewski	Gromadzenie danych, sprawdzanie i edycja manuskryptu	1%	
Hubert Suszek	Metodologia, sprawdzanie i edycja manuskryptu	1%	
Marcin Wojnar	Koordynacja, sprawdzanie i edycja manuskryptu	1%	
Maciej Kopera	Opracowanie założeń pracy, metodologia, pisanie pierwszej wersji pracy, nadzór	3%	

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