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CLINICAL INVESTIGATION

Connected consciousness after tracheal intubation in young adults: an international multicentre cohort study

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Abstract

Background: Connected consciousness, assessed by response to command, occurs in at least 5% of general anaesthetic procedures and perhaps more often in young people. Our primary objective was to establish the incidence of connected consciousness after tracheal intubation in young people aged 18–40 yr. The secondary objectives were to assess the nature of these responses, identify relevant risk factors, and determine their relationship to postoperative outcomes.
Methods: This was an international, multicentre prospective cohort study using the isolated forearm technique to assess connected consciousness shortly after tracheal intubation.
Results: Of 344 enrolled subjects, 338 completed the study (mean age, 30 [standard deviation, 6.3] yr; 232 [69%] female). Responses after intubation occurred in 37/338 subjects (11%). Females (13%, 31/232) responded more often than males (6%, 6/106). In logistic regression, the risk of responsiveness was increased with female sex (odds ratio [$OR_{adjusted}$]=2.7; 95% confidence interval [CI], 1.1–7.6; P=0.022) and was decreased with continuous anaesthesia before laryngoscopy ($OR_{adjusted}$=0.43; 95% CI, 0.20–0.96; P=0.041). Responses were more likely to occur after a command to respond (and not to nonsense, 13 subjects) than after a nonsense statement (and not to command, four subjects, P=0.049).
Conclusions: Connected consciousness occured after intubation in 11% of young adults, with females at increased risk. Continuous exposure to anaesthesia between induction of anaesthesia and tracheal intubation should be considered to

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reduce the incidence of connected consciousness. Further research is required to understand sex-related differences in the risk of connected consciousness.

Keywords: awareness; consciousness; general anaesthesia; isolated forearm technique; memory; recall; sex; tracheal intubation

Editor's key points

- Intraoperative consciousness without explicit recall under general anaesthesia, known as connected consciousness, is much more common than explicit recall.
- In this multicentre study, the isolated forearm technique was used to assess of connected consciousness shortly after tracheal intubation in young adults.
- Responses consistent with connected consciousness occurred in 37 of 338 subjects (11%), and were twice as likely to occur in female (13%) than in male (6%) subjects.
- Further research is required to determine whether continuous anaesthetic exposure between induction of anaesthesia and tracheal intubation reduces the incidence of connected consciousness, and to understand the sex-related differences.

General anaesthesia is a state of unconsciousness and unresponsiveness, and explicit recall of intraoperative events is rare (0.1–0.2%).[1–4] However, intraoperative consciousness without explicit recall occurs more often. 'Connected consciousness' involves the experience of environmental stimuli, whereas 'disconnected consciousness', such as dreaming, does not.[5,6] Our recent study suggests that connected consciousness without recall occurs in at least 5% of patients[6,7]; earlier studies report it in up to 42% of patients.[8–10] When surveyed, 60% of people felt it was unacceptable to be aware of intraoperative events even if they could not recall them afterwards.[11] Furthermore, implicit recall of intraoperative events has been associated with reduced postoperative satisfaction, dysphoria, and post-traumatic stress disorder.[3,6,12] In order to assess connected consciousness independent of memory, we used the isolated forearm technique.[8]

Although a 5% rate of intraoperative connected consciousness is more than an order-of-magnitude higher than the incidence of consciousness with explicit recall, a subgroup analysis of our earlier study[6] suggested the rates are even higher in patients younger than 40 yr (10/75, 13%; 95% confidence interval [CI], 7–22 compared with 2/185, 1.1%; 95% CI, 0.2–3 in patients older than 40 yr; odds ratio [OR]=14; 95% CI, 3–66; unpublished data). Herein we sought to identify the incidence of connected consciousness after tracheal intubation in young adults using the isolated forearm technique. We also analysed potential risk factors including whether sex is a risk factor for connected consciousness during anaesthesia, as suggested by the observations of reduced time to awakening of females on intended emergence from general anaesthesia.[13–15] Interestingly, case reviews of consciousness with explicit recall demonstrate sex differences,[2,16,17] but this is rarely evident in prospective cohort studies.[1,3,4] Additionally, we investigated whether continuous exposure to anaesthesia (volatile or intravenous) between induction and tracheal intubation was associated with a reduction in the incidence of connected consciousness.

We also sought to better understand the nature of the isolated forearm technique (IFT) response. To address a criticism that hand responses may be reflexive, and not volitional, we assessed the response to a command (to 'squeeze my hand') *vs* a syllable-matched statement. Subjects were asked whether they were experiencing pain. We used a forced-choice word retrieval task to determine whether responses are associated with implicit memory. Lastly, we assessed the association of responses with explicit recall of intraoperative events and postoperative delirium.

Methods

This international, multicentre cohort study was carried out at 10 tertiary and quaternary hospitals (UW Health University Hospital, NewYork-Presbyterian / Weill Cornell Medical Center, Hospital of the University of Pennsylvania, Rambam Health Care Campus, Liège University Hospital, Cairns Hospital, Munich University Hospital, Auckland City Hospital, University Hospital RWTH Aachen and Waikato Hospital). Each site obtained ethical approval from their own Institutional Review Board, with the University of Wisconsin performing the initial review (2017–0728, August 2017) and clinical trial registration (NCT03503357). The study was supported by departmental resources. Patients 18–40 yr old undergoing general anaesthesia with tracheal intubation were recruited to participate. Patients were excluded if they were unable to sign consent, to speak the local language, or participate in all parts of the study (e.g. a contraindication to placing the sphygmomanometer such as lymphoedema). Patients undergoing rapid sequence induction of anaesthesia were also excluded from the study. For each subject, preoperative and induction medications were administered at the discretion of the attending anaesthetist. Data from each site were entered into the Research Electronic Data Capture (REDCap) database[18] hosted by the University of Wisconsin Institute for Clinical and Translational Research. We initially planned to recruit 500 subjects to (1) provide an accurate estimate of the incidence of IFT responses in young people (assuming a 13% incidence, we would determine a 95% CI between 10% and 16%) and (2) observe at least 50 occurrences of responsiveness to allow the evaluation of moderate-sized effects in up to five risk factors. Statistical analyses were conducted using R Statistical Software (version 4.0.3; R Foundation for Statistical Computing, Vienna, Austria).

Primary outcome

We used the IFT to assess connected consciousness as described.[8] Briefly, a sphygmomanometer cuff was inflated on the forearm to prevent the hand from being paralysed during neuromuscular block. Subjects were read a series of commands, statements, and words beginning 10 s after tracheal intubation (Supplementary Figs S1 and S2). Commands were read aloud by the research team, except at one study centre where commands were recorded and delivered by earphones. A hand squeeze in response to verbal command or nonsense statement was considered a response, indicating connected consciousness. Subjects who initiated a hand squeeze to any of the commands or nonsense statements were counted as responders. Subjects with hand clenching in response to laryngoscopy (and before the verbal cues) were not counted as responders unless an additional squeeze was initiated during the verbal cues. The IFT assessor was not blinded to the anaesthetic medications administered. A statistical analysis plan was approved by the authors before analyses began, in consultation with the study statistician (BK). Specifically, exposures of interest were chosen based on our *a priori* hypothesis that age, sex, and continuous exposure to anaesthesia before laryngoscopy influence responsiveness. Mixed-effects logistic regression was used to correlate these risk factors with IFT responsiveness while adjusting for site as a random effect. Significance was assessed using likelihood ratio tests.

Secondary outcomes

Using a crossover design, the first two statements after tracheal intubation were randomised as (1) a command to squeeze the researcher's hand and (2) a syllable matched statement (with no command; Supplementary Fig. S2). These paired nominal data were analysed using McNemar's exact test. Subsequent statements assessed verbal comprehension ('if stones float on water, squeeze my hand') and whether or not the subjects were experiencing pain ('if you are in pain squeeze my hand two times'). Subjects who initiated a hand squeeze after a statement or command (and before the next statement or command) were counted as responding to that item. To assess implicit and explicit memory, subjects were presented 16 target words during the IFT command sequence. At 60 min after arrival to the recovery unit, memory was assessed using the two-alternative first choice signal detection method. Subjects were presented with a pair of words; one a target word and the other a foil.[19] The subjects were asked to select the word that seemed more familiar, or otherwise to choose randomly. The word pairs were balanced for linguistic characteristics and were not phonetically or phonemically similar.[20,21] For counterbalancing and to avoid position effects, alternate versions of the command sequence and retrieval sequence were created and applied randomly (Supplementary Fig. S3). Word retrieval data was analysed by logistic regression using IFT response with age and sex as covariates.

Explicit memory was assessed by administering a modified Brice questionnaire 60 min after arrival to the recovery unit and again 7 days after surgery.[22] Questionnaire reports were categorised as 'unlikely', 'possible', or 'definite' based on the detail of the description and its relation to events that occurred while under anaesthesia by a group of three anaesthesiologist members of the study team. The assessors were not blinded to the subject's IFT response. Postoperative delirium was assessed using the Nursing Delirium Screening Scale (Nu-DESC) at 15 and 30 min into postoperative recovery by a member of the research team. Scores ≥2 were considered positive for delirium.[23]

Demographic, medical history, and anaesthetic information were recorded for all subjects. Anxiety and pain were quantified using a 0–10 numeric rating scale. Heterogeneity in medications administered, dose, and timing relative to laryngoscopy required some decisions in how to quantify the data. The induction dose for each medication includes all administrations between induction and laryngoscopy. Propofol dose is reported in mg kg^{-1} based on total body weight. The time between induction and laryngoscopy is the time between the first bolus of propofol, etomidate, or ketamine, and laryngoscopy. Any subject who received a volatile anaesthetic, propofol infusion, or intermittent propofol boluses between induction and laryngoscopy was categorised as having received 'continuous anaesthesia'. For univariate associations with responsiveness, count data were compared using ORs from a Fisher's exact test. Continuous and ordinal data were summarised as median (inter-quartile [IQR]) and compared using Wilcoxon signed-rank tests.

Results

Recruitment was stopped early owing to funding constraints. Of 344 subjects who enrolled, 338 received general anaesthesia with tracheal intubation and completed the study (Fig 1). Responses occurred in 37 out of 338 subjects (11%; 95% CI, 8–15). The characteristics of responders and non-responders are reported in Table 1 and Supplementary Table S1. Although 13% of females responded (31/232), only 6% of males responded (6/106; OR=2.6; 95% CI, 1.01–7.8). Other patient details, ASA physical status, and comorbid diseases were similar among responders and non-responders. Administration and dosing of induction medications, time between induction and laryngoscopy, and number of attempts at laryngoscopy were similar between responders and non-responders. No subject in either group underwent more than three intubation attempts. Because females were more likely to respond than males, we also quantified these characteristics according to sex (Supplementary Table S2). Females did not receive less propofol during induction (2.1; IQR, 1.8–2.6 mg kg^{-1}) than males (2.3; IQR, 1.8–2.8 mg kg^{-1}; difference, −0.2; 95% CI, −0.3 to 0.0). Similar results were found when subjects were grouped by both sex and IFT response (Supplementary Fig. S4). Other characteristics were similar between females and males.

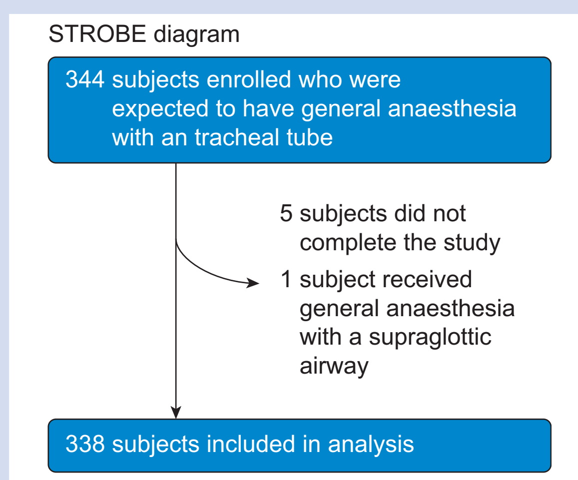

Fig 1. STROBE diagram. STROBE, Strengthening The Reporting of OBservational Studies in Epidemiology.

Table 1 Characteristics of isolated forearm technique responders and non-responders. One subject who did not receive propofol for induction received etomidate. Ten subjects were intubated without the administration of a neuromuscular blocking drug. ASA, American Society of Anesthesiologists; CI, confidence interval; IQR, inter-quartile range; NMBD, neuromuscular blocking drug.

	Responders		Non-responders		Or [95% CI]	Difference [95% CI]
	n (%)	Median (IQR)	*n* (%)	Median (IQR)		
Age (yr)		33 (27–36)		31 (25–36)		−1.0 [−2.9, 1.0]
Sex						
Female	31		201		2.6 [1.01, 7.8] female *vs* male	
Male	6		100			
BMI (kg m^{-2})		28 (23–39)		26 (24–33)		−0.9 [−3.7, 1.7]
ASA physical status		1 (1–2)		2 (1–2)		0.0 [0.0, 0.0]
Preoperative						
Anxiety		3 (2–5)		3 (2–6)		0.0 [−1.0, 1.0]
Pain		1 (1–2.5)		1 (1–3)		0.0 [0.0, 0.0]
History of awareness during anaesthesia	1 (2.7)		4 (1.3)		2.0 [0.04, 22]	
Chronic medications						
Beta-blocker	2 (5.4)		7 (2.3)		2.4 [0.23, 13]	
Total medications		1 (0–2.75)		1 (0–2)		0.0 [−1.0, 0.0]
Induction medications						
Benzodiazepine (mg)						
Alprazolam	1 (2.7)	0.5	8 (2.6)	0.5 (0.5–0.5)	1.0 [0.0, 8.1]	0
Midazolam	16 (43.2)	2 (2–2)	151 (50.1)	2 (2–2)	0.85 [0.1, 39]	0.0 [0.0, 0.0]
Opioid (μg)						
Alfentanil	0		1 (0.3)	750		
Fentanyl	23 (64.9)	100 (50–200)	193 (64.1)	100 (100–150)	0.9 [0.4, 2.0]	0.0 [−49, 25]
Remifentanil	0		14 (4.6)	200 (163-2400)	0.0 [0.0, 2.5]	
Sufentanil	9 (24.3)	10 (10–15)	76 (25.2)	20 (15-20)	1.0 [0.4, 2.2]	5.0 [0.0, 9.9]
Propofol (mg kg^{-1})	37 (100)	2.1 (1.8–2.5)	300 (99.7)	2.2 (1.8–2.7)		0.1 [−0.1, 0.3]
Ketamine (mg) NMBD (mg)	2 (5.4)	43 (35–50)	6 (3.3)	25 (21–25)	2.8 [0.3, 16]	−19 [−10, −30]
Atracurium	2 (5.4)	30 (30–30)	15 (5.0)	35 (30–40)	0.9 [0.1, 4.0]	5.0 [-5.0, 20]
Rocuronium	32 (86.5)	50 (40–50)	229 (76.0)	50 (40–50)	1.9 [0.7, 6.6]	0.0 [0.0, 0.0]
Vecuronium	2 (5.4)	8.5 (8–9)	16 (5.3)	7 (6–8)	1.0 [0.1, 4.6]	−1.8 [−5.0, 4.0]
Succinylcholine	1 (2.7)	100	16 (5.3)	110 (100–152)	0.5 [0.1, 3.4]	10 [0.0, 100]
Continuous anaesthetic exposure	13 (35.1)		164 (54.5)		0.5 [0.2, 0.98]	
Time between induction and laryngoscopy (s)		240 (185–293)		226 (186–288)		−9.0 [−39, 19]
Laryngoscopy attempts		1 (1–1)		1 (1–1)		0.0 [0.0, 0.0]
Movement in response to laryngoscopy	28 (75.7)		126 (41.9)		4.2 [1.8, 10.7]	

Logistic regression identified that females were more likely to respond than males ($OR_{adjusted}$=2.7; 95% CI, 1.1–7.6; P=0.022; Table 2). Subjects with exposure to continuous anaesthesia before laryngoscopy were less likely to respond ($OR_{adjusted}$=0.43; 95% CI, 0.20–0.96, *P*=0.043). However, age was not predictive ($OR_{adjusted}$=1.1; 95% CI, 0.76–1.6; *P*=0.60; odds are for a 1 standard deviation [SD] age difference; 1 SD=6.3 yr).

There were 24 subjects who responded to one of the first two paired statements after tracheal intubation. Subjects responded only to command (13/338, 3.8%) more often than only to the nonsense statement (4/338, 1.2%; 7/338, 2.1%, responded to both command and nonsense statements; 13+4+7=24; *P*=0.049; Table 3). Thirteen subjects did not respond to one of the first two paired statements but did respond to subsequent statements (24+13=37 responders total), and 18 out of 37 (49%) responders endorsed being in pain by responding to 'If you are in pain, squeeze my hand two times'. Fewer subjects responded to each of the remaining items: five subjects extended two fingers when prompted by verbal command, four subjects correctly responded to a statement such as 'If fish swim in the sea, squeeze my hand', and three subjects incorrectly responded to a statement such as 'If stones float on water, squeeze my hand'.

Word retrieval scores for responders (8; IQR, 7–9) and non-responders (8; IQR, 7–10) were not significantly different when adjusted for age and sex (*P*=0.52; Table 4). A score of 8 would be equivalent to random chance on the 16-question, forced-choice word retrieval task.

On the modified Brice questionnaire, 23 subjects endorsed connected consciousness and 48 subjects endorsed having disconnected consciousness (dreams) while under anaesthesia. Of these, eight subjects endorsed having both connected and disconnected consciousness. An additional three subjects did not endorse connected consciousness, but described events that may have occurred between induction and emergence. On review, most reports were considered unlikely cases of connected consciousness with explicit recall because they were vague, described dreams, or described events that occurred before or after surgery. There were five reports considered possible cases and one report considered a definite case of explicit recall. Thus, the observed incidence of possible explicit recall was 1.5% (95% CI, 0.6–3.2) and of definite explicit recall

Table 2 Predictors of isolated forearm technique responsive. Logistic regression analysis with age, sex, and continuous anaesthetic exposure as predictors and with site as a fixed predictor of connected consciousness. Odds ratios (ORs) for age are reported for 1 SD in age difference (6.3 yr). CI, confidence interval; SD, standard deviation.

	Responder	Non-responder	$OR_{adjusted}$ [95% CI]	P-value
Age (yr, mean, SD)	31.1 (5.9)	30.2 (6.4)	1.1 [0.76, 1.6]	0.60
Sex (*n*)				
Female	31	201	2.7 [1.1, 7.6]	0.022
Male	6	100	female vs male	
Continuous anaesthetic exposure (%)	35.1	54.5	0.43 [0.20, 0.96]	0.041
Site (*n*)				
1	2	23		
2	2	18		
3	4	14		
4	1	12		
5	2	35		
6	2	14		
7	12	38		
8	2	32		
9	3	47		
10	7	68		

was 0.3% (95% CI, 0.03–1.3). Two of the subjects with possible explicit recall described the post-intubation IFT testing, but only one of these subjects responded during IFT testing. Table 5 describes the possible and definite cases of explicit recall.

Delirium was present in 14% of responders (5/37) and 7% of non-responders (22/301) at 15 min into recovery. At 30 min into recovery, delirium persisted in only 3% of responders (1/37) and 4% of non-responders (11/301). Responders were not significantly more likely to exhibit delirium at either 15 min (OR=2.0; 95% CI, 0.5–5.9) or 30 min (OR=0.7; 95% CI, 0.0–5.3).

Discussion

We assessed the incidence, risk factors, and postoperative implications of connected consciousness in 338 subjects, making it the largest cohort of its type. Connected consciousness without recall occurred after tracheal intubation in 11% of procedures conducted in young adults. This is higher than the incidence reported in older adults (4.6%),[6] and is 100-fold higher than the incidence of explicit recall of intra-operative events.[1–4] Post-intubation connected consciousness occurred across all 10 international study sites. There were no differences in medical comorbidity, dosing of anaesthetic drugs, or performance of tracheal intubation to explain why some subjects experienced connected consciousness.

Females were more than twice as likely to experience connected consciousness as males. This surprising finding does not seem to be attributable to the recruitment of younger subjects or biased administration of anaesthetic medications. Differences in dosing, if present, were small and do not explain why females experienced connected consciousness more often than males. Alternatively, there may be biological differences in sensitivity to anaesthetic drugs. Indeed, females may be more likely to have connected consciousness with explicit memory formation during anaesthesia,[2,7] although these reports are not universal and sex was not considered a risk factor in a critical review of the literature.[24] Similarly, some findings suggest that females require larger doses of anaesthetics,[25] but others disagree.[26,27] In either case, our dosing data show that anaesthesiologists do not perceive females as relatively insensitive to anaesthetics or at risk for connected consciousness (with or without recall). Considering the incidence of intraoperative connected consciousness and the millions of anaesthetics performed each year, there is an urgent need for further research into differences in anaesthetic sensitivity between the sexes.

Subjects who received continuous anaesthesia were less likely to experience connected consciousness, consistent with our previous findings.[6] It is important to note that connected consciousness occurred during the delivery of standard care, as anaesthetics were administered at the discretion of the attending anaesthetist. Often, induction and intubation are separated by a few minutes, during which some practitioners

Table 3 Response to command *vs* nonsense statement. The first two statements after intubation were delivered in random order: a command and a syllable-matched statement with no command (nonsense). Subjects were more likely to respond to command (P=0.049, McNemar's exact test).

	Response to nonsense	No response to nonsense
Response to command	7	13
No response to command	4	314

Table 4 Association of isolated forearm technique responses with implicit memory. Linear regression analysis with isolated forearm technique response, age, and sex as predictors of word retrieval task score. Coefficient for age is reported for 1 SD in age difference (6.3 yr). CI, confidence interval; SD, standard deviation.

	Coefficients [95% CI]	P-value
Isolated forearm technique response	0.2 [−0.5, 0.9]	0.52
Age	1.1 [0.8, 1.6]	0.13
Sex	−1.8 [−0.5, 0.4] Female *vs* male	0.73

Table 5 Responses considered to represent definite or possible cases of awareness during anaesthesia. Descriptions summarise the experience endorsed by the subject. Parentheses may include additional details relating the experience to events that occurred in the perioperative period. F, female; IFT, isolated forearm technique; M, male.

Age (yr) and sex	Induction drug	Surgery	Description	Interview reported	Determination	Reported dreams	IFT
31, F	Propofol	Segmental lung resection	Endorsed trying and being unable to speak. Remembered staff talking about the tissue and whether someone who was married or not. (Report correlated with tissue samples taken during surgery and OR conversation.)	In recovery, At 1 week	Definite	N	N
40, F	Propofol	Laparoscopic cholecystectomy	Endorsed the study team reading words and feeling pain with the incision. (The subject did not recall specific words or OR events.)	In recovery, At 1 week	Possible	Y	Y
21, M	Propofol	Laparoscopic appendectomy	Endorsed feeling warm gel on his stomach and a vague recollection of 'being shaved on my stomach, but it felt different to how I shave my face — more like hairs being pulled out'. (The subject was prepped with *cold* prep and shaved before incision. The subject was unsure whether this was a dream.)	In recovery, At 1 week	Possible	Y	N
28, M	Propofol	Coblation of lingual tonsil	Endorsed a vague experience of someone holding his hand and caressing his head during surgery.	In recovery, At 1 week	Possible	Y	Y
28, F	Propofol	Laparoscopic ovarian cystectomy	Endorsed being asked to squeeze the hand of the research team 'either just before or during surgery'.	In recovery	Possible	N	N
31, F	Propofol	Laparoscopic sleeve gastrectomy	Endorsed a vague memory of people above her and being unable to move. She felt aware that she was in surgery. The subject also described looking down at herself as she laid on the operating table.	In recovery, At 1 week	Possible	N	N

will administer additional anaesthetics. Based on our prior study,[6] and validated here, we propose that provision of continuous anaesthesia is a simple practical approach to reduce the incidence of connected consciousness. Procedural difficulty might considerably increase the time between induction and tracheal intubation, in which case it is common to administer additional anaesthetics. We stress that consciousness did not occur as the result of delayed or difficult intubation, as there was no difference in time to laryngoscopy or number of attempts at laryngoscopy between responders and non-responders.

Selection of only young adults curtailed the power of this study to observe an age-related difference. Based on our previous study we expected connected consciousness in 13% (95% CI, 7—22) of subjects in this age group and observed 11% (95% CI, 8—15), suggesting concordance (unpublished data). The incidence of pain reported with IFT responses was also consistent with our prior study (42%[5] *vs* 49% herein).

Although the occurrence of intraoperative connected consciousness without recall is not considered controversial,[24] some question the relevance of a response to the IFT. If subjects are more likely to respond to a command than a nonsense statement, multiple cortical areas are processing the auditory cue and coordinating a motor response. Indeed, several subjects were able to extend two fingers in response to a verbal command. Volitional response is considered the gold standard in consciousness research. Many responders were capable of experiencing and endorsing pain. In our opinion, this is a higher level of consciousness than patients (or their anaesthesiologists) anticipate during general anaesthesia. However, it is reassuring that connected consciousness does not necessarily lead to explicit recall of the experience. We also did not observe implicit recall of the experience, as both responders and non-responders scored similarly on the word retrieval task. Still, implicit recall has been documented in certain conditions during general anaesthesia[28] and could occur during episodes of connected consciousness as measured by IFT responses. Lastly, connected consciousness was not associated with an increase in postoperative delirium.

The most significant limitations of this study were the limitations in assessing connected consciousness. Although we assessed IFT responses after tracheal intubation, connected consciousness might occur throughout an anaesthetic and might occur more frequently during maintenance of anaesthesia.[10] Indeed, we observed cases of connected consciousness with explicit recall that were not associated with IFT responsiveness after intubation. This might confound our findings, particularly on the postoperative impact of connected consciousness. IFT responses were also heterogeneous. For instance, some subjects began to respond part way through the list of statements, missing the first two paired statements. Others responded to the first statements, but then stopped responding. This heterogeneity, compounded by an early end to recruitment, limited our evaluation of the nature of IFT responses. Assessing responses to a series of commands and nonsense statements (as opposed to a single command) may have increased the incidence of connected consciousness observed in this study compared with previous studies. IFT verbal cues were generally read aloud, and responses were assessed by the research team member performing the IFT testing. In the future, verbal commands could be recorded and measurement of IFT responses could be automated. Finally, a positive IFT response can be interpreted as fulfilling the gold standard metric for consciousness, a behavioural response, but interpretation of a negative response is less clear. A lack of response can reflect lack of motivation, comprehension, or distraction (e.g. by pain) as well as unconsciousness or sensory disconnection. Multiple methods, in addition to the IFT, will likely be required to identify consciousness under anaesthesia.

Additional limitations relate to the nature of observational work and the possibility of unknown bias or confounding. This was partly mitigated by the multicentre design and randomisation of commands. Most subjects underwent induction of anaesthesia with propofol, limiting the generalisability of our findings to other methods of induction. Although limiting the age range allowed us to focus on young people and observe more instances of responsiveness, it limited our ability to assess age as a risk factor for connected consciousness.

In summary, our data suggest that the incidence of connected consciousness without recall after intubation in young adults is more than an order-of-magnitude greater than connected consciousness with explicit recall. Females appear at particular risk, with nearly a threefold increase in the odds of responding. These results are not adequately explained by drug dosing and suggest new approaches are required to prevent consciousness under anaesthesia.

Authors' contributions

Study design: KOP, AR, VB, PS, GS, MM, MC, JR, AD, RR, AP, MK, JS, AG, RDS
Data collection: all authors except JR and BK
Data analysis: RL, AR, BK, RDS
Drafting of the manuscript: RL, RDS
All authors revised and gave approval for the final version of the manuscript.

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Declarations of interest

AR serves as a consultant for Medtronic and Neuroindex. RDS is a member of the editorial board of the *British Journal of Anaesthesia*. The other authors have no potential conflicts of interest to disclose.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bja.2022.04.010.

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