Dissociating speech perception and comprehension at reduced levels of awareness

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We used functional MRI and the anesthetic agent propofol to assess the relationship among neural responses to speech, successful comprehension, and conscious awareness. Volunteers were scanned while listening to sentences containing ambiguous words, matched sentences without ambiguous words, and signal-correlated noise (SCN). During three scanning sessions, participants were nonsedated (awake), lightly sedated (a slowed response to conversation), and deeply sedated (no conversational response, rousable by loud command). Bilateral temporal-lobar responses for sentences compared with SCN were observed at all three levels of sedation, although prefrontal and premotor responses to speech were absent at the deepest level of sedation. Additional inferior frontal and posterior temporal responses to ambiguous sentences provide a neural correlate of semantic processes critical for comprehending sentences containing ambiguous words. However, this additional response was absent during light sedation, suggesting a marked impairment of sentence comprehension. A significant decline in postscan recognition memory for sentences also suggests that sedation impaired encoding of sentences into memory, with left inferior frontal and temporal lobe responses during light sedation predicting subsequent recognition memory. These findings suggest a graded degradation of cognitive function in response to sedation such that “higher-level” semantic and mnemonic processes can be impaired at relatively low levels of sedation, whereas perceptual processing of speech remains resilient even during deep sedation. These results have important implications for understanding the relationship between speech comprehension and awareness in the healthy brain, in patients receiving sedation and in patients with disorders of consciousness.

Anesthesia | functional MRI | language | memory | sedation

As anyone who has tried to converse with a drowsy partner can testify, spoken language comprehension appears to be severely impaired at reduced levels of awareness. This impairment is difficult to assess behaviorally, because it is possible that speech comprehension remains intact, but the ability to produce spoken responses or to remember speech is impaired. Such a phenomenon may have parallels in two clinical situations: first, patients diagnosed as in a vegetative state (VS) or minimally conscious state may comprehend some or all speech but may be unable to report the fact because of impaired motor responses (1, 2). Indeed, near-normal neural responses in such patients have been reported in association with tests of speech comprehension (3). Second, some patients undergoing surgery under general anesthesia may comprehend some or all of what is going on around them. However, unless specific techniques are used, patients may be unable to signal that comprehension was intact or remember speech for later report (4). Such phenomena might suggest that speech can be both perceived and comprehended in the absence of conscious awareness or subsequent memory. However, functional imaging studies have so far failed to answer whether higher cognitive processing of speech is preserved in the absence of conscious awareness and have not provided neural correlates of the transition between conscious and nonconscious perception of spoken language.

In the present study, we tested the hypothesis that perceptual and semantic processes that contribute to speech comprehension and memory encoding can be differentially affected at reduced levels of awareness. We use functional imaging during graded sedation with an anesthetic agent to assess neural correlates of covert language comprehension at reduced levels of awareness. Previous functional MRI (fMRI) studies of volunteers under the influence of anesthetic agents have suggested that the additional activity normally observed in awake volunteers when speech is compared with matched nonspeech sounds is not observed after sedation or anesthesia (5, 6). What is unclear is whether this absence of speech-specific activity during anesthesia also implies a lack of comprehension. Neural responses observed in sedation-induced low awareness states may also assist interpretation of responses to speech in VS and minimally conscious state patients. It is unclear whether neural activity that has been observed in some patients implies intact perception and comprehension of speech (2).

We used fMRI in conjunction with well controlled speech and nonspeech materials (7) to assess neural responses to speech sounds and sentence meaning during sedation with the anesthetic agent propofol. By comparing responses to sentences and acoustically matched nonspeech noises (signal-correlated noise, SCN), we can assess activity in regions of the superior and middle temporal gyri involved in perceiving spoken sentences while controlling for low-level auditory processes that are engaged for all sounds (compare refs. 8 and 9). To assess neural responses to sentence meaning, we contrast responses to sentences that contain ambiguous words (such as bark or rain/reign) with matched sentences that lack equivalent ambiguities. Ambiguous words are ubiquitous in spoken language (10), and an additional process of contextually constrained meaning selection is necessary for successful comprehension of sentences that contain an ambiguous word (11, 12). Existing work has highlighted bilateral inferior frontal and left posterior inferior temporal regions, which show an elevated response to sentences containing ambiguities (7, 13). In the present study, we use this neural correlate


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Abbreviations: VS, vegetative state; fMRI, functional MRI; SCN, signal-correlated noise; IFC, inferior frontal gyrus; MTG, middle temporal gyrus; PCG, precentral gyrus; FDR, false discovery rate.

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of ambiguity resolution as a marker for intact sentence comprehen-
sion, which we can then assess at reduced levels of awareness.

In previous fMRI studies using propofol sedation, the drug was administered at a single infusion rate (6) or by a computer-
controlled infusion system with a single “target” plasma con-
centration in all volunteers (5). In contrast, we individually
tailored propofol infusion rates to generate specific levels of
sedation in each of three scanning runs in each volunteer.
Sedation levels were systematically assessed by using spoken
response guided by the Ramsay sedation scale (14). Such ratings
have previously shown a high degree of interrater reliability and
therefore provide a systematic well validated measurement scale
for the assessment of awareness levels (15). We assessed speech-
specific perceptual processes and higher-level semantic pro-
cesses at three qualitatively different levels of sedation: nonse-
dated (awake), lightly sedated (a slowed response to
conversation), and deeply sedated (no conversational response
but rouseable by loud commands).

**Results**

**Speech Perception and Comprehension.** Contrasting BOLD
responses to SCN and silence (SCN vs. silence) highlighted activity
in primary auditory regions on the superior temporal plane,
centered on Heschl’s gyrus. As shown previously (5, 6), auditory
responses compared with a silent baseline are robust at all three
levels of sedation tested, demonstrating that cortical auditory
processes remain functional during sedation [see Fig. 1 a–c and
supporting information (SI) Table 1]. To assess speech-specific
neural responses, we contrast the BOLD response to low-
ambiguity sentences and SCN (low vs. SCN). Consistent with
previous fMRI findings in awake volunteers (7, 9), this contrast
highlights anterior and posterior regions in the superior and
middle temporal gyri (Fig. 1d; SI Table 2) that support perceptual
processes critical for speech comprehension (16, 17). We
also observe an additional response to speech in inferior frontal
and premotor regions. A striking finding, however, is that the
response of both temporal- and frontal-lobe regions remains
robust in lightly sedated volunteers (Fig. 1e). Despite particip-
ants showing no response to conversational speech once deeply
sedated, temporal (but not frontal) responses to speech remain
largely intact (Fig. 1f).

Neural correlates of semantic processes involved in sentence
comprehension were assessed by using the contrast between
responses to high- and low-ambiguity sentences (high vs. low).
The previous findings of inferior frontal and inferior temporal
activity in this contrast are replicated for awake volunteers (Fig.
1g; SI Table 3). However, despite speech-specific activity in both
lightly and deeply sedated volunteers, the contrast between high-
and low-ambiguity sentences did not reveal any significant
difference in activity even during light sedation (Fig. 1h).

The interaction between condition (SCN, low- and high-
ambiguity sentences) and sedation (awake, light, and deep
sedation) reveals a number of left-lateralized regions that show
a condition-specific response to sedation, including the middle
temporal, precentral, and inferior frontal gyri (see Fig. 2a; SI
Table 4). As confirmed by paired comparisons, not all brain
areas show the same condition by sedation interaction, and thus
we observe dissociations among regions showing a progressive
reduction of perceptual and semantic responses to speech at
reduced levels of awareness (see Fig. 2b–d; SI Table 5 and SI Fig.
4). For instance, the inferior frontal gyrus (IFG; Fig. 2b) shows
a significant decline in the ambiguity effect (high vs. low)
between awake and light sedation conditions but no reduction in
perceptual responses to speech (low vs. SCN) during light
sedation. In contrast, the middle temporal gyrus (MTG; Fig. 2c)
and precentral gyrus (PCG; Fig. 2d) show a significant reduction
in speech responses (low vs. SCN) during light sedation. Com-
paring the ambiguity response (high vs. low) during light and
deep sedation fails to reveal any brain area that shows a
significant decline in semantic processing. However, we do see a
further decline in activity for speech (low vs. SCN) in all three
regions mentioned previously (IFG, MTG, and PCG), although
this fails to reach false discovery rate (FDR)-corrected signifi-
cance in the MTG. Statistical comparison of the response
profiles of the three peak voxels in the IFG, MTG, and PCG plotted
in Fig. 2b–d reveal a significant three-way brain region
by condition by sedation interaction (P < 0.01) with paired
comparisons of pairs of regions confirming that the response of
The IFG is significantly different from both the MTG and PCG, which did not differ from each other. These three regions thus show differential condition-specific responses to sedation.
when responses were assessed only for sentences that were subsequently recognized.

Discussion

We demonstrate a graded and hierarchical reduction in the recruitment of processes involved in speech perception and comprehension with increased sedation. In awake and fully conscious participants, fMRI activation provides evidence for processes engaged in perceiving speech sounds, computing the meaning of ambiguous spoken sentences and encoding these sentences for subsequent memory. During light sedation, activity associated with speech–sound perception remained robust, yet recognition memory for sentences was variable and activity related to semantic ambiguity processing was absent. At the deepest level of sedation tested, participants were often difficult to rouse, showed substantially impaired responses to conversational speech, and were unable to encode sentences for subsequent memory. These observations are consistent with substantially impaired awareness of sentences presented during deep sedation. However, cortical activation was still observed for speech sounds in regions of the MTG that have previously been ascribed a critical role in speech perception (8, 9, 16, 17). Although there have been reports of temporal-lobe responses for participants’ names compared with beeps during sleep (21) and for nonattended sentences compared with nonattended background noise (22), our work goes beyond these reports by demonstrating significant changes in neural responses associated with changes in awareness of speech sounds and by assessing neural correlates of semantic and mnemonic processing of sentences at declining levels of awareness.

Neural Correlates of Perceptual Awareness of Speech. We believe the changes we observe in speech-specific responses between light and deep sedation provide a neural correlate of the transition between conscious and nonconscious perception of speech. We observed a striking change in the magnitude of inferior frontal and premotor responses to speech; these are both areas that have been previously associated with speech perception (9, 23–25). Studies that have demonstrated neural responses to speech in the absence of awareness, during sleep (21), or for nonattended presentations (22) report activity that is confined to the temporal lobe. This is consistent with the temporal-lobe responses that we observed during deep sedation. Our data go beyond these previous reports, however, in suggesting a direct association between reduced activity in prefrontal and premotor regions and reduced awareness of speech.

The association between conscious awareness for spoken materials and activity in frontal and premotor regions suggested by the current results is consistent with fMRI responses to brief masked presentations of written words, which can similarly evoke posterior cortical activity in conjunction with reduced prefrontal and premotor activation (26). However, whereas masked visual presentation also produces a marked reduction in activity in posterior regions involved in perceptual processing (such as the fusiform gyrus), temporal-lobe responses for speech compared with SCN during deep sedation remained robust and showed only marginal reductions relative to light sedation. Thus, in our work, as in another recent study of the neural basis of visual consciousness (27), frontal activity is most clearly associated with conscious awareness, and posterior regions show smaller changes in activity despite significant changes in the degree of conscious awareness. Such findings are consistent with a global-workspace account (28) in which conscious awareness for speech is supported both by activity in specific frontal systems and through coherent or synchronous activity in distributed frontotemporal regions.

Semantic and Mnemonic Processing of Speech at Reduced Levels of Awareness. What is the role of conscious awareness in comprehension and memory for speech stimuli? This issue has previously been explored by examining behavioral and neurophysiological responses to speech that is outside the focus of attention. Listeners attending to one channel of dichotically presented speech can detect whether the nonattended channel contains speech or nonspeech sounds but fail to notice whether nonattended speech changes to a foreign language (29). Nonetheless, unattended words attract our attention, such as when one’s name is called, a “mixture party effect” that suggests some words are recognized in unattended speech (30), and recent behavioral work has demonstrated repetition priming effects from nonconsciously perceived words (31, 32). Mismatch negativity studies have shown evoked electrophysiological responses that vary with the lexical, semantic, and syntactic properties of isolated words in the absence of directed attention (33). However, in our work, neural correlates of ambiguity resolution, a process that is critical for successful comprehension, were significantly reduced and abolished even by light sedation with propofol. This finding suggests that propofol sedation produces an impairment in speech comprehension consistent with both reduced recognition-memory performance and slower and more hesitant verbal interactions during light sedation.

Our results provide evidence for an association between speech comprehension (as indexed by ambiguity-related activity) and awareness level. This may arise because the rapid efficient disentangling of semantic ambiguity requires coordinated activity in anatomically distant frontal and temporal regions, and these long-range functional interactions are highly susceptible to sedation. Previous observations of frontal and temporal cortical responses for the contrast of high- vs. low-ambiguity sentences in VS patients (2, 3) are therefore likely to be of great clinical significance. This conclusion is supported by the recent observation that one patient who fulfilled clinical criteria for VS demonstrated both sensitivity to semantic ambiguity and showed changes in neural activation in response to spoken instructions (3). Whether semantic ambiguity resolution can proceed in the absence of conscious awareness in healthy nonsedated volunteers remains unclear. Further research to assess neural correlates of ambiguity resolution in other low-awareness states, such as during dichotic speech presentation or using MMN paradigms, would be valuable.

Recognition-memory performance remained above chance for sentences presented during light sedation, even while activity related to semantic ambiguity processing was absent. This may indicate that participants can remember sentences they initially failed to comprehend, and indeed we think that above-chance performance on the recognition-memory test could arise solely from familiarity with the perceptual form of heard words. In future studies, foil sentences that include a previously unused meaning of an ambiguous word could be used in the recognition-memory test to assess this possibility. However, given the complete failure of recognition memory for sentences presented during deep sedation, despite speech-specific responses in the temporal lobe, the present results confirm that neural correlates of perceptual processing of speech can remain intact even in the absence of subsequent memory for speech content.

Implications for Anesthesia. Our results provide direct evidence of differential dose-dependent effects of i.v. anesthetics on the hierarchy of cortical processing required for speech comprehension. The dissociations we have observed among perceptual, semantic, and mnemonic responses to speech during sedation demonstrate that anesthetic agents affect cognitive function in a graded fashion. Higher-level processes involved in computing the meaning of sentences or encoding them into memory can be affected at relatively low levels of sedation, whereas lower-level
perceptual processing of speech remains intact. These results support the view that anesthesia is a behavioral and neural continuum rather than a discrete event. This conclusion has potentially important implications for how patients with low residual blood concentrations of anesthetic drugs receive postoperative instructions. For instance, we saw a significant decline in left IFG activity in response to high-ambiguity sentences at sedation levels that produce only a moderate impairment in conversational speech. Impaired sentence comprehension may be particularly relevant (both clinically and medicolegally) in the context of ambulatory surgery, where patients are discharged home without formal clinical supervision after short surgical procedures under general anesthesia.

Our findings are also highly relevant to the phenomenon of awareness under anesthesia (34, 35), typically diagnosed when patients report postoperative recollection of events occurring during general anesthesia. Anesthetic awareness is a distressing complication with an overall incidence of 0.1–0.2% after surgery and a significantly greater incidence in patients undergoing cardiac surgery, cesarean section, and trauma surgery. Our results show that post-sedation memory is correlated with activity in left frontal and temporal regions that have been associated with successful memory encoding of verbal materials in awake participants (36, 37). A previous positron-emission tomography study assessing the effect of propofol on resting cerebral blood flow has shown increased hippocampal activity during sedation (38). However, the present data are equivocal as to whether activity in hippocampal regions serves to support residual sentence memory during light sedation. Our observations may provide a neur-anatomical substrate for successful memory encoding of speech overheard during anesthesia. The implied connections between the neuroimaging literature on memory encoding and postanesthetic recall provide a basis for further research on this clinically important topic.

Current electroencephalographic monitoring of anesthetic depth may significantly reduce awareness by providing neurophysiological targets for titration of anesthesia (34). However, the neurophysiological targets used for such titration have so far been validated against a definition of awareness, which includes explicit postoperative recollection of events. Such a definition may underestimate the true incidence of complex cortical processing of speech, because our data show that speech-specific neural activity in lateral temporal regions may occur without subsequent memory. The paradigms we have used may provide one way of calibrating anesthetic monitors, so that drug administration can be titrated to also prevent comprehension and both one way of calibrating anesthetic monitors, so that drug administration can be titrated to also prevent comprehension and both conscious and unconscious perception of speech, rather than just subsequent recollection, thus satisfying both doctors' and patients' expectations concerning general anesthesia.

**Methods**

Participants and Paradigm. Twelve right-handed English-speaking volunteers participated in the experiment (nine male); mean (range) age was 34 (29–42) years, mean (range) mass was 70 (52–85) kg. All participants were medically trained anesthetists who gave written informed consent under the guidance of the Cambridge Local Research Ethics Committee in accordance with the Helsinki declaration.

We used the stimulus materials and experimental design from a recent fMRI study (7). There were two experimental conditions in which spoken sentences were presented: 59 high-ambiguity sentences containing two or more ambiguous words (e.g., “there were dates and pears in the fruit bowl”) and 59 well matched low-ambiguity sentences without ambiguous words (e.g., “there was beer and cider on the kitchen shelf”) (for further information, see ref. 7). An additional 59 sentences matched for duration and number of syllables and words were converted to speech-spectrum SCN (compare with ref. 39) using Praat software (www.praat.org). These stimuli have the same spectral profile and amplitude envelope as the original speech but are entirely unintelligible. An additional 60 silent trials were also included to allow comparisons between responses to non-speech SCN and silent rest. These trials were divided into three runs of 79 trials with different conditions presented in a pseudorandom order. The order of the three runs was counterbalanced, so that different stimulus items were presented at each of three levels of sedation (nonsedated, lightly sedated, and deeply sedated) in different volunteers.

After participants were removed from the scanner, and the sedative effects of propofol had worn off, a sentence-recognition-memory test was administered to 11 of the participants. This consisted of a written list of 236 sentences, including the 59 high- and 59 low-ambiguity sentences. Participants were asked to indicate which sentences they recognized having heard during scanning. Hit and false-alarm responses were analyzed to derive a signal-detection measure of sentence recognition-memory performance (d'), which corrects for biases induced by participants that respond consistently “yes” or “no” when unsure.

Sedation Procedure. The 12 volunteers were scanned in three 12-min fMRI sessions, while nonsedated (awake), lightly sedated (Ramsay score 2; ref. 14), and deeply sedated (Ramsay score 3), using propofol. Propofol is a GABA potentiating compound commonly used by i.v. infusion for sedation during surgical procedures and intensive care. In higher doses, it is used for induction and maintenance of general anesthesia. In the present study, we used a manually implemented “effect-site steering” algorithm in conjunction with a computer-controlled infusion pump to achieve step-wise increments in the sedative effect of propofol. This method allowed us to individually tailor propofol infusion rates to generate specific levels of sedation for scanning runs in each volunteer (for further details, see SI Text).

Before each scanning run, we assessed participants’ level of sedation by talking to them through the headphone and microphone system in the scanner and judged their level of sedation according to their verbal responses. Before administration of propofol, volunteers were fully awake, alert, and responsive, and thus could not be scored on the Ramsay sedation scale, which is intended for patients in an intensive care setting. During administration of propofol, participants become more relaxed and slowed in their responses to conversations, although without obvious slurring or impairment in conversation, consistent with level 2 on the Ramsay scale. Once participants no longer spontaneously engaged in conversation and responded in a slurred and impaired voice to loud commands or to their name being shouted, we deemed them to be at Ramsay 3. The mean (range) estimated effect-site propofol concentration was 1.0 (0.5–1.3) μg/ml during light sedation (Ramsay 2) and 1.5 (0.8–2.5) μg/ml during deep sedation (Ramsay 3). Mean (range) total mass of propofol administered was 231 (131–342) mg, equivalent to 3.4 (1.9–5.4) mg/kg. The variability of these concentrations and doses is typical for studies of the pharmacokinetics and pharmacodynamics of propofol.

Because of the time taken to recover from propofol sedation, it was not practical to fully counterbalance the order of the three sedation levels in different participants. Data were acquired in the following order: nonsedated, Ramsay 2, Ramsay 3 in 9 of 12 volunteers; and nonsedated, Ramsay 3, Ramsay 2 in the remaining three participants. Statistical comparisons of experimental and control data demonstrate that scan order effects are insufficient to account for observed effects of sedation (see SI Text).
Three-way brain region by condition by sedation-level interactions were entered into repeated-measures ANOVAs. Significant parameter estimates from peak voxels in the condition by sedation interaction were characterized by specific responses at different sedation levels. Parameter estimates of multi-voxel parameter estimates in neural activity and cannot be explained by effects of scan order (41). Condition-specific effects of propofol sedation detected by i.v. anesthetics such as propofol have no major direct effects on neural activity and cannot be explained by effects of scan order (42). i.v. Condition-specific effects of propofol sedation detected by i.v. anesthetics such as propofol have no major direct effects on neural activity and cannot be explained by effects of scan order (41). Condition-specific effects of propofol sedation detected by i.v. anesthetics such as propofol have no major direct effects on neural activity and cannot be explained by effects of scan order (41). Condition-specific effects of propofol sedation detected by i.v. anesthetics such as propofol have no major direct effects on neural activity and cannot be explained by effects of scan order (41). Condition-specific effects of propofol sedation detected by i.v. anesthetics such as propofol have no major direct effects on neural activity and cannot be explained by effects of scan order (41).
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