versions of SNAP-25 that mimic cleavage by BoNT/A (residues 1 to 197) were reconstituted into vesicles (with 15% PS). As a control, a truncated version of SNAP-25 that mimics cleavage by BoNT/E (corresponding to residues 1 to 180), was tested in parallel [this cleavage event results in a more profound block of exocytosis (13)]. Fusion was abolished by the “BoNT/E” truncation (Fig. 4B). In contrast, the “BoNT/A” truncation supported a low level of fusion that could be enhanced by increasing [Ca2+]: the Ca2+ response was too impaired to determine the precise [Ca2+]1/2, but this value is >360 μM (Fig. 4B). Thus, the reconstituted system recapitulates the functional effect of BoNT/A and E treatment on neurons (13, 19, 20).

Membrane-embedded synt has been reported to stimulate membrane fusion in a Ca2+-independent manner (21). We have repeated these experiments and observed the same phenomena. The lack of an effect of Ca2+ is surprising, because the ability of synt to interact with its targets in the reduced fusion assay is promoted by Ca2+. The easiest explanation, however, is that the bacterially expressed full-length synt is not fully functional. Variants of a number of isoforms of synt, including synt I, that lack a transmembrane domain are expressed in cells where they may also regulate membrane traffic in vivo, supporting the idea that studies with the cytoplasmic domain of synt are physiologically relevant (22–24).

The data reported here indicate that a complex of synt, membranes, and SNARE proteins forms the core of the Ca2+-triggered fusion apparatus. With this reconstitution approach, it should be possible to test additional factors to construct a Ca2+-triggered membrane fusion complex that operates on the rapid (millisecond) time scale observed during synaptic transmission.

References and Notes
10. Detailed materials and methods are available as supporting material on Science Online.
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Integration of Word Meaning and World Knowledge in Language Comprehension

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Although the sentences that we hear or read have meaning, this does not necessarily mean that they are also true. Relatively little is known about the critical brain structures for, and the relative time course of, establishing the meaning and truth of linguistic expressions. We present electroencephalogram data that show the rapid parallel integration of both semantic and world knowledge during the interpretation of a sentence. Data from functional magnetic resonance imaging revealed that the left inferior prefrontal cortex is involved in the integration of both meaning and world knowledge. Finally, oscillatory brain responses indicate that the brain keeps a record of what makes a sentence hard to interpret.

Language is used, among other things, to exchange information about the world. This entails that, during online comprehension, the meaning of a phrase or sentence is derived and, in many cases, its truth is verified. For this to be possible, usually information about the words of a language and about the facts of the world need to be retrieved from memory.

At least since Frege (1, 2), theories of meaning have made a distinction between the semantics of an expression and its truth value in relation to our mental representation of the state of affairs in the world (3, 4). For instance, the sentence “the present queen of England is divorced” has a coherent semantic interpretation, but it contains a proposition that is false in the light of our knowledge in memory that she is married to Prince Phillip. The situation is different for the sentence “the favorite palace of the present queen of England is divorced.” Under default interpretation conditions, this sentence has no coherent semantic interpretation, because the predicate is-divorced requires an animate argument. This sentence mismatches with our representation of the world in memory, because the descriptive features of the purported state of affairs are inherently in conflict. The difference between these two sentences suggests the distinction that can be made between facts of the world and facts of the words of our language, including their meaning. Although theories of semantic memory usually do not make this distinction (5), accounts of online language processing often do, and they distinguish between the retrieval and usage of world knowledge and of knowledge of word meaning.

Relative to the distinction between facts of the world and facts of the words of one’s language, some aspects of word meaning might be characterized as linguistic in nature, whereas other aspects relate to world knowledge. In linguistic theory, the latter is referred to as the domain of pragmatics, and the former as the domain of semantics. Based on

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invoking world knowledge (meaning can only be fully established by cause many words are polysemous, and their meaning can only be fully established by invoking world knowledge). Researchers have pointed out that the distinction between linguistic meaning and world knowledge is problematic because many words are polysemous, and their meaning can only be fully established by invoking world knowledge.

We decided to contribute to settling this issue by providing neurophysiological evidence on the integration of semantic and world knowledge information. The underlying idea is that if a principled distinction can be made between linguistic meaning and world knowledge, concomitant processing differences should be observed during the interpretation of a sentence.

This study presents electroencephalogram (EEG) and functional magnetic resonance imaging (fMRI) data that speak to this issue. While participants’ brain activity was recorded, they read three versions of sentences such as “the Dutch trains are yellow/white/sour and very crowded” (the critical words are in italics). It is a well-known fact among Dutch people that Dutch trains are yellow, and therefore the first version of this sentence is correctly understood as true. However, the linguistic meaning of the alternative color term white applies equally well to trains as the predicate yellow. It is world knowledge about trains in Holland that makes the second version of this sentence false. This is different for the third version. This version contains a violation of semantic constraints. The core meaning of sour is related to taste and food. Under standard interpretation conditions, a predicate requires an argument whose semantic features match that of its predicate. For our third sentence, this is clearly not the case, because semantic features related to taste and food do not apply to trains. One could thus argue that for semantic internal reasons, the third sentence is false or incoherent (3,12). It is our knowledge about the words of our language and their linguistic meaning that pose a problem for the interpretation of the third version of this sentence.

The increased interpretation load of semantic and world knowledge violations is assumed to have an effect on electrophysiological brain activity and on the hemodynamic response. If semantic interpretation precedes verification against world knowledge, the effects of the semantic violations should be earlier and might invoke other brain areas than the effects of the world knowledge violations.

Based on EEG recordings from 29 electrode sites (13,14), event-related brain potentials (ERPs) were computed and time-locked to the onset of the critical words that embodied the semantic violation, the world knowledge violation, and their correct counterpart. ERPs reflect the summation of the postsynaptic potentials of a large ensemble of synchronously active neurons. They provide a sampling of the brain’s electrical activity with a very high temporal resolution. We focused on one particular ERP effect, referred to as the N400. The amplitude of this negative-going ERP between roughly 250 and 550 ms, with a maximum at ~400 ms, is influenced by the processing of semantic information (15). The easier the match between the lexical semantics of a particular content word and the semantic specification of the context, the more reduced the N400 amplitude will be. The N400 is known to be very sensitive to semantic integration processes (16, 17).

As expected, the classic N400 effect was obtained for the semantic violations. For the world knowledge violations, we also observed a clear N400 effect. Crucially, this effect was identical in onset and peak latency and was very similar in amplitude and topographic distribution to the semantic N400 effect (Fig. 1). This finding is strong empirical evidence that lexical semantic knowledge and general world knowledge are both integrated in the same time frame during sentence interpretation, starting at ~300 ms after word onset.

In addition, we used the EEG data to investigate oscillatory brain activity in a wide frequency range (1 to 70 Hz) in relation to the semantic and world knowledge violations. Amplitude increases of EEG oscillations in specific frequency bands, such as theta (4 to 7 Hz) and gamma (~30 to 70 Hz), that are induced by a cognitive event are thought to reflect the dynamic recruitment of the relevant neuronal networks engaged in cognitive processing (18). A wavelet-based time-frequency representation (TFR) of EEG power changes (Fig. 2) revealed a clear gamma peak for the world knowledge violation that was not seen for the semantic violation (19). In contrast, relative to the other conditions, the semantic violation resulted in an increase in power in the theta frequency range. Both effects are visible within the latency range of the N400. Especially at lower frequencies (e.g., at theta frequencies), the temporal resolution of the wavelet transform is relatively poor. This implies that the relative onset difference between theta and gamma activity cannot be taken as a reliable indicator of onset differences in the underlying neurophysiological events. In particu-
The common activation for semantic and world knowledge violations compared to the correct condition, based on the results of a minimum T-field conjunction analysis (supporting online text). Both violations resulted in a single common activation ($P = 0.043$, corrected) in the left inferior frontal gyrus, in or in the vicinity of BA 45 (with coordinates $[x, y, z] = [-44, 30, 8]$ and $Z = 4.87$) and BA 47 ($[x, y, z] = [-48, 28, -12]$, $Z = 4.15$). The cross-hair indicates the voxel of maximal activation and has coordinates $[x, y, z] = [-44, 30, 8]$ (left BA 45). L, left hemisphere; R, right hemisphere.

In conclusion, while reading a sentence, the brain retrieves and integrates word meanings and world knowledge at the same time. The LIPC is a crucial area for this integration process. Moreover, it does not take longer to discover that a sentence is untrue than to detect it is semantically anomalous. However, the oscillatory brain responses suggest that the brain keeps a record of what makes a sentence hard to interpret, whether this is word meaning or world knowledge.

References and Notes

Complete Genome Sequence of the Apicomplexan,
Cryptosporidium parvum

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The apicomplexan Cryptosporidium parvum is an intestinal parasite that affects healthy humans and animals, and causes a unrelenting infection in immunocompromised individuals such as AIDS patients. We report the complete genome sequence of C. parvum, type II isolate. Genome analysis identifies extremely streamlined metabolic pathways and a reliance on the host for nutrients. In contrast to Plasmodium and Toxoplasma, the parasite lacks an apicoplast and its genome, and possesses a degenerate mitochondrion that has lost its genome. Several novel classes of cell-surface and secreted proteins with a potential role in host interactions and pathogenesis were also detected. Elucidation of the core metabolism, including enzymes with high similarities to bacterial and plant counterparts, opens new avenues for drug development. Cryptosporidium parvum is a globally important intracellular pathogen of humans and animals. The duration of infection and pathogenesis of cryptosporidiosis depends on host immune status, ranging from a severe but self-limiting diarrhea in immunocompetent individuals to a life-threatening, prolonged infection in immunocompromised patients. A substantial degree of morbidity and mortality is associated with infections in AIDS patients. Despite intensive efforts over the past 20 years, there is currently no effective therapy for treating or preventing C. parvum infection in humans.

4. Although for Frege (3), reference was established relative to objects in the world, here we follow Jackendoff’s suggestion (3) that this is done relative to objects and the state of affairs as mentally represented.
11. Often word meanings can only be fully determined by individuals to a life-threatening, prolonged self-limiting diarrhea in immunocompetent immune status, ranging from a severe but neglected intracellular pathogen of humans and animals.
13. ERPs for 30 subjects were averaged time-locked to the onset of the critical words, with 40 items per condition.

Sentences were presented word by word on the center of a computer screen, with a stimulus onset asynchrony of 600 ms. While subjects were reading the sentences, their EEG was recorded and amplified with a high-cut-off frequency of 70 Hz, a time constant of 8 s, and a sampling frequency of 200 Hz.

Materials and methods are available as supporting material on Science Online.

19. We obtained TFRs of the single-trial EEG data by convolving the complex Morlet wavelets with the EEG data and computing the squared norm for the result of the convolution. We used wavelets with a 7-cycle width, with frequencies ranging from 1 to 70 Hz, in 1-Hz steps. Power values thus obtained were expressed as a percentage change relative to the power in a baseline interval, which was taken from 150 to 0 ms before the onset of the critical word. This was done in order to normalize for individual differences in EEG power and differences in baseline power between different frequency bands. Two relevant time-frequency components were identified: (i) a theta component, ranging from 4 to 7 Hz and from 300 to 800 ms after word onset, and (ii) a gamma component, ranging from 35 to 45 Hz and from 400 to 600 ms after word onset.

24. Whole brain T2*-weighted echo planar imaging blood oxygen level-dependent (EPI-BOLD) fMRI data were acquired with a Siemens Sonata 1.5-T magnetic resonance scanner with interleaved slice ordering, a volume repetition time of 2.48 s, an echo time of 40 ms, a 90° flip angle, 31 horizontal slices, a 64 × 64 slice matrix, and isotropic voxel size of 3.5 × 3.5 × 3.5 mm. For the structural magnetic resonance image, we used a high-resolution (isotropic voxels of 1 mm3) T1-weighted magnetization-prepared rapid gradient-echo pulse sequence. The fMRI data were preprocessed and analyzed by statistical parametric mapping with SPM99 software (http://www.fil.ion.ucl.ac.uk/spm99).

References and Notes
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Cryptosporidium parvum belongs to the phylum Apicomplexa, whose members share a common apical secretory apparatus mediating locomotion and tissue or cellular invasion. Many apicomplexans are of medical or veterinary importance, including Plasmodium, Babesia, Toxoplasma, Neospora, Sarcocystis, Cyclospora, and Eimeria. The life cycle of C. parvum is similar to that of other cyst-forming apicomplexans (e.g., Eimeria and Toxoplasma), resulting in the formation of oocysts.