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Caffeine, Priming, and Tip of the Tongue: Evidence for Plasticity in the Phonological System

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A study was performed involving phonological priming and tip-of-the-tongue states (TOTs) in which participants took either 200 mg of caffeine or placebo. Results show a clear positive priming effect produced for the caffeine group when primed with phonologically related words. When primed with unrelated words, the caffeine subgroup produced a significant increase in the number of TOTs. This contrasting effect provides evidence that the positive priming of caffeine was not a result of caffeine's well-known alertness effects. For placebo, a significant negative effect occurred with the related-word priming condition. The results support the novel hypothesis that the blocking of A_1 adenosine receptors by caffeine induces an increased short-term plasticity effect within the phonological retrieval system.

Tip of the tongue (TOT) is a common form of word retrieval failure that is accompanied by a feeling of knowing the word. It is usual that someone in this state can access the semantic and syntactic form of the word and possibly some of its phonological properties (e.g., the initial sound or exact number of syllables). The precise phonological form remains inaccessible (Bock & Levelt, 1994; Caramazza, 1997). There have been many studies investigating the effect of priming and cueing on TOTs that have yielded contrasting results. For example, a number of experiments showed that it was more likely that TOTs were overcome when participants were cued with the initial letter of a target word than when cues were phonologically different (Brennan, Baguely, Bright, & Bruce, 1990; Freedman & Landauer, 1966; Gruneberg & Monks, 1974; Pease & Goodglass, 1978). Similar results were seen when whole words that rhymed with the target were used as cues (Kozlowski, 1977). However, Jones (1989) and Jones and Langford (1987), by presenting interloper words while participants retrieved the response to dictionary definitions, found a larger number of TOTs when interloper words were phonologically related to the target word, as compared with unrelated or semantically related interlopers. However, Perfect and Hanley (1992) suggested that the results of these studies could have been due to a facilitation effect of responses that without the interloper could well have resulted in "don't know" responses. Also, Jones and Jones and Langford did not pair definitions in the phonologically related interloper condition without phonologically related interlopers or with the absence of interlopers. Consequently, TOTs induced with the presentation of phonologically related interlopers could occur simply because certain definitions induced more TOTs even without the interlopers. Therefore, Perfect and Hanley performed an experiment using the same definitions as Jones and showed that even when no interlopers were presented, more TOTs were induced. They also showed that when definitions were matched for the number of TOTs they induced, no effect of interloper words was seen. They concluded that under these controlled conditions there was no evidence supporting the results of Jones or Jones and Langford. Thus, different studies have found differing and sometimes contradictory results concerning the effects of priming and cueing of phonologically related words and the occurrence of TOTs, but the overall agreement is that externally presented primes or cues when phonologically related to a target aid its retrieval.

However, results from some of these studies could have been attributed to strategic retrieval processes. On the basis of a paradigm designed to eliminate retrieval or guessing strategies, it was still shown that the prior production of phonologically related words (priming) reduced the number of TOTs for the target word (answer to general knowledge question; James & Burke, 2000). It has been shown that the mechanism responsible for improved target retrieval remained active for some tens of seconds and occurred without the awareness of the participant. Typical neural network short-term memory models, such as the pattern-buffering properties of recurrent collateral networks or synfire chain systems, are not usually considered to have sufficiently long time courses to account for a priming effect lasting several tens of seconds (Durstewitz, Seamans, & Sejnowski, 2000). Instead, we speculate that the reported priming effect can be accounted for by transient modifications of neuronal responses of pyramidal cells mediated by cellular mechanisms (i.e., by neuronal adaptation). The present study seeks to investigate this hypothesis.

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Short-Term Plasticity

Various forms of short-term plasticity (STP) have been implicated in hippocampal and neocortical information processing (Egorov, Hamam, Fransen, Hasselmo, & Alonso, 2002; Fisher, Fischer, & Carew, 1997) and have speculatively been proposed as mechanisms that may underpin higher order function in neocortex (Fisher et al., 1997). Two promising neurobiological mechanisms that may account for a weak priming effect over the time scale demonstrated by the psychological paradigm of James and Burke (2000) include augmentation and posttetanic potentiation (PTP; Anwyl, Lee, & Rowan, 1988). These are both types of STP. Augmentation grows and decays with a time scale of 5–10 s and PTP lasts from 5 s to several minutes (Fisher et al., 1997). These two mechanisms of enhancement are attributed to effects of residual elevation in cytoplasmic Ca^{2+} involving the presynaptic terminals (Carter, Vogt, Foster, & Regehr, 2002; Dittman, Kreitzer, & Regehr, 2000). All phases of enhancement for pyramidal cells are accompanied by an increase in frequency of spontaneous postsynaptic potentials (PSPs; Zucker & Regehr, 2002). It was found in experiments on slice preparations of the stratum radiatum region of CA1 in response to stimulation from the Schaffer collaterals (Anwyl et al., 1988; Lee, Anwyl, & Rowan, 1987) that both an augmentation and a PTP effect on the amplitude of extracellular PSPs occurred. These are summarized in Figure 1. Comparing these results to the likely situation for human cortical pyramidal cells, a cell with a tuned receptive field for a particular "behavioral" stimulus may briefly respond with a rate calculated from the first few interspike intervals at about 200 Hz, but it is unlikely to average more than 100 Hz for the duration of the stimulus presentation (Crick & Asanuma, 1986; Lynch, Mountcastle, Talbot, & Lin, 1977). We speculate that cells tuned to a particular stimulus may possibly undergo some STP, whereas cells with less selectivity for the stimulus may not respond enough to evoke STP or may evoke STP only at a reduced level.

In summary, PTP and augmentation occur only in active cells, increasing in degree as activity increases. This means that a paradigm that selectively increases activity should increase the responsiveness of the selected cells through enhanced STP. Under the assumption that neuronal representations for the phonologically related primes are significantly correlated with the neuronal representations for the retrieval target, then priming should selectively activate STP in cells mediating recall of the target, thus actively facilitating retrieval when priming is related.

However, some other well-known neural adaptation effects seem to reduce the responsiveness of cells, at least when stimulated with long-constant current input (Lanthorn, Storm, & Andersen, 1984; Wang, 1998). If this effect holds for behaviorally realistic conditions, a plausible interpretation of the effect would be that a reduction in the responsiveness of tuned cells to a particular stimulus potentially causes an accommodation effect found in some repetition-priming and cueing studies. This effect is manifest as a *deficit* in responding to a target that is related to the prime as opposed to a facilitation effect. These effects seem to be a function of the duration of the prime–target interval. Many

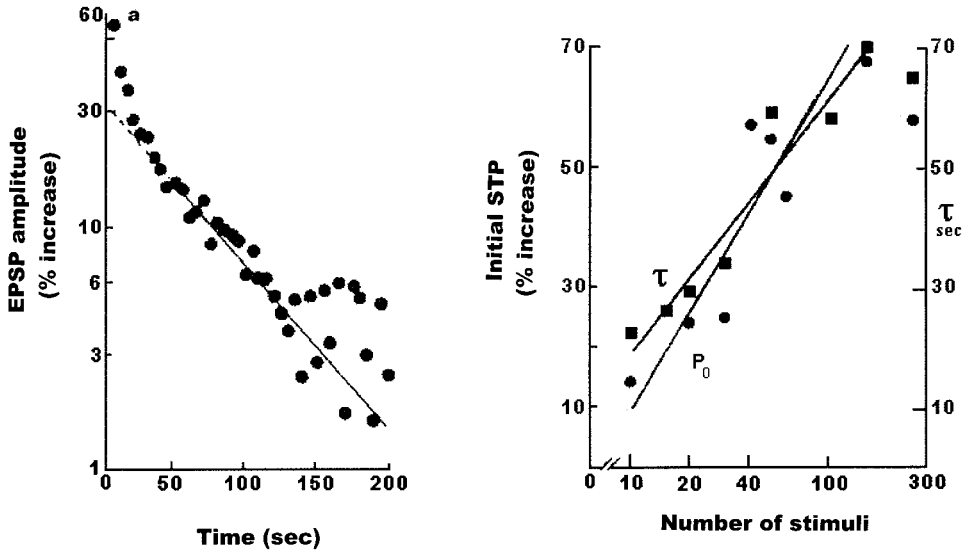

Figure 1. Left panel: Graph shows typical time course of enhanced potentiation following a 75-pulse tetanus delivered at 250 Hz. The intercept of the dashed line with the *y*-axis shows the estimated initial short-term plasticity (STP). The characteristically higher responses (above this line) over the first 20 s show augmentation, a more rapidly decaying stronger temporary increase. EPSP = excitatory postsynaptic potentials. Right panel: Circles denote magnitude of induced increase in initial STP for an increasing number of pulses. Squares denote the decay-time constant of STP, τ. We expect that, in as much as this evidence of STP may carry over to awake-behaving humans, then typical conditions are likely to equate to the left-hand side of this graph where it is noticeable that it required about 10 pulses to elicit any STP for which about a 10% increase was found. From "The Role of Calcium in Short-Term Potentiation in the Rat Hippocampal Slice," by R. Anwyl, W.-L. Lee, and M. Rowan, 1988, *Brain Research, 459*, p. 193. Adapted with permission of Elsevier Science B. V.

studies have investigated the effect of timing between prime onset and target onset with concrete findings. For example, Huber, Shiffrin, Lyle, and Ruys (2001) provided evidence for both a facilitation effect and a negative effect for repeated words. They performed a two-alternative forced choice study in which two words were presented (either related to the target or related to a foil), a target word was seen briefly, then a mask, and finally two words that the participant had to make a decision about, stating which was the target word seen previously. Passively viewed primes of short duration (500 ms) resulted in a strong preference to choose the word that had been primed. However, when the duration increased to 2,000 ms, there was a preference *against* choosing repeated words. Similar findings of this short-duration facilitation and long-duration deficits in priming of related stimuli have been shown in many domains. These include visual (Busey & Loftus, 1994; Dixon & Di Lollo, 1994), 3D perceptual (Long, Toppino, & Mondin, 1992), face perception (Leopold, O'Toole, Vetter, & Blanz, 2001), semantic (Smith & Klein, 1990), affective (Murphy & Zajonc, 1993), and attentional (Taylor & Klein, 1998). According to Huber and O'Reilly (2003), the facilitatory effect is interpreted as neural persistence, a residual prime activation, followed by neural accommodation, a lessening of the facilitation that they explain by synaptic depression. The opposite pattern is expected for unrelated stimuli (i.e., when an item is strongly activated it will inhibit unrelated competitors, but this inhibition will decrease when accommodation occurs).

Thus a pharmacological manipulation that can enhance STP without significantly enhancing neural adaptation/accommodation may provide insight into the neurobiological bases of the positive phonological priming effects seen in previous TOT studies (Brennan et al., 1990; Freedman & Landauer, 1966; Gruneberg & Monks, 1974; James & Burke, 2000; Pease & Goodglass, 1978).

Caffeine

Caffeine is known to have multiple effects at the cellular level. It is well known that caffeine causes an increase in cytoplasmic calcium ion levels by eliciting a significant increase of calcium release from intracellular stores (but not from stores in the postsynaptic dendrites; Chou, Khan, Ford, & Hirsch, 1985; Greene, Haas, & Hermann, 1985; Kuba & Nishi, 1976; Lee et al., 1987; Neering & McBurney, 1984). It also inhibits cyclic nucleotide phosphodiesterases (Fredholm, 1980) and blocks $GABA_A$ receptors (Akopian, Gabriel, & Witkovsky, 1998). However, these effects only occur when caffeine concentration levels are much higher than those found in typical consumption, which for Italians is approximately 210 mg/day, on average (Fredholm, Bättig, Holmén, Nehlig, & Zvartu, 1999). At these levels, the blocking effects of caffeine on the adenosine A_1 and A_{2a} receptors predominate, as shown in Figure 2. The A_{2a} receptors are found in dopamine receptor-rich brain areas (see Fredholm et al., 1999, for a review), whereas the A_1 receptors are widely expressed, with high levels found in the neocortex (Fastbom, Pazos, & Palacios, 1987; Goodman & Snyder, 1982). The A_1 receptors mediate inhibition of transmitter release from the presynaptic cell and limit the activity-evoked membrane depolarization on the postsynaptic cell (Rudolphi, Schubert, Parkinson, & Fredholm, 1992). This control of neuronal excitability can be affected by caffeine, as caffeine competitively binds with these A_1 receptors, preventing the inhibition and causing subsequent excitation. In particular, Greene et al. (1985) carried out a slice preparation experiment on pyramidal cells in the rat CA1. They found that even at low concentration levels of caffeine, starting from about 10 μM there was an increase in excitatory postsynaptic potentials, a decrease in membrane resting potential, and a reduction of the long afterhyperpolarization. This amount relates directly to human blood plasma levels after consumption of 200 mg of caffeine as shown in Figure 2. In Lee et al. (1987), it was shown that caffeine reduced augmentation and PTP. This effect was attributed to Ca^{2+} depletion caused by caffeine. However these results were found for caffeine levels of 0.5–10 mM. These levels, several hundred times that found in average daily caffeine consumption, are toxic in humans (Fredholm et al., 1999). Typical consumption of approximately 200 mg of caffeine (about two cups of coffee) provides a dose of approximately 0.8–5.0 mg of caffeine per kg, roughly corresponding to blood plasma concentrations of 2–20 μM. At these concentration levels, as can be seen from Figure 2, caffeine's effect on the A_1 and A_{2a} receptors predominates.

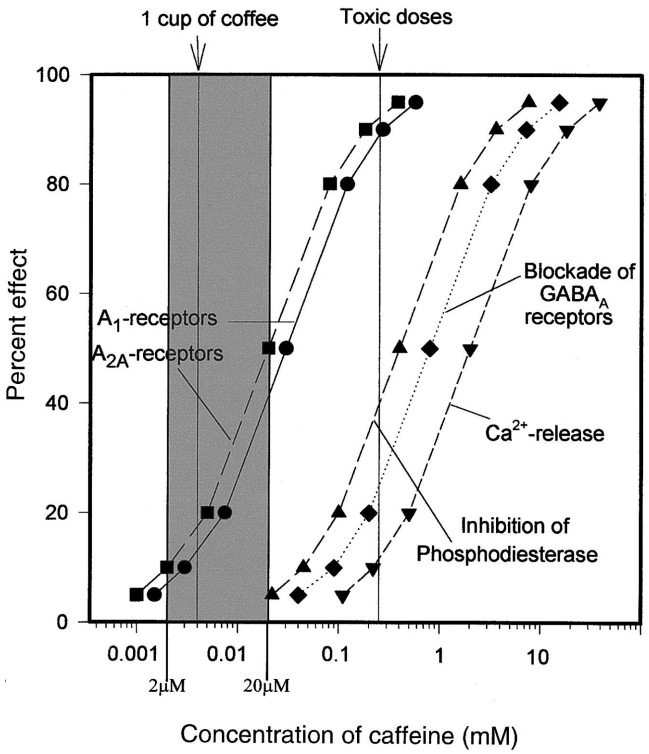

Figure 2. The shaded area shows the blood plasma concentration levels reached when 200 mg of caffeine is administered to human participants. Levels reach approximately 2–20 μM, and at these concentration levels, caffeine's effect on the A_1 and A_{2A} receptors predominates. GABA = gamma aminobutyric acid. From "Actions of Caffeine in the Brain With Special Reference to Factors That Contribute to Its Widespread Use," by B. B. Fredholm, K. Bättig, J. Holmén, A. Nehlig, & E. E. Zvartu, 1999, *Pharmacological Reviews, 51,* p. 88. Adapted with permission of the American Society for Pharmacology and Experimental Therapeutics.

Present Study

A study was performed using a similar paradigm as that of James and Burke (2000), with the addition of caffeine as a phar-

macological agent. The STP account of the effect of priming on the TOT phenomenon suggests that the group given the questions primed by the related word list would show a significant reduction in the number of TOTs for the caffeine subgroup as compared with the placebo group. Such a result could be explained by enhanced augmentation and PTP strengthening the priming effect. Conversely, for the caffeine subgroup given the question primed with the unrelated list (i.e., no phonological overlap), there should be a less significant reduction in the number of TOTs. If the action of caffeine is selective only in the related prime case, then the action of caffeine on the task cannot easily be attributed to some general activation/attention effect and is therefore likely to be caused by the effects of caffeine on the neuronal system subserving phonological retrieval. If the participants primed with the unrelated list show a significant increase in the number of induced TOTs for the caffeine subgroup, the results support the speculation that caffeine enhanced augmentation and PTP is actively interfering with the retrieval process by the phonological priming of words unrelated to the target.

A recent study using a repetition-priming paradigm and pharmacological modification suggested GABAergic and cholinergic systems mediate a priming effect (Thiel, Henson, Morris, Friston, & Dolan, 2001). However, this study investigated the effects of several repetitions of primes approximately 40 min before the test phase and is thus not related to the short-term effects of priming considered here. Further, an earlier related study (Miller & Desimone, 1993) using a similar time course to ours (a few tens of seconds) found no evidence for the involvement of cholinergic mechanisms in the specific region (anterior–ventral inferior temporal cortex) thought to be involved in the repetition-priming mechanism studied in Thiel et al. (2001).

Experiment 1

Method

Participants. Sixty-four native Italian speakers took part in the experiment. They were, on average, 24.0 ($SE = 0.3$) years old and had 16.5 ($SE = 0.1$) years of education. Smokers were excluded, as were people who consumed more than 400 mg of caffeine per day. Women who were pregnant or taking contraceptive pills were also excluded. Participants abstained from alcohol for 24 hr and from caffeine for 12 hr prior to testing. Nicotine, pregnancy, and contraceptive pills are known to affect the half-life of caffeine in the body (Lieberman, 1992), whereas alcohol remains potentially active for a longer period of time. We wished to minimize the effects of alcohol on the paradigm. A between-subjects design was used, as pilot studies showed a low return rate for the second session.

Ethics. Ethics approval was granted by the Scuola Internazionale Superiore di Studi Avanzati (SISSA) Ethics Committee, Trieste, Italy, and the participants were paid for their contribution.

Materials. One hundred general knowledge questions, each answered by a single low-frequency word (the target), were compiled. For each question, a list of 10 prime words was constructed. As in James and Burke (2000), two separate lists of prime words were used: related and unrelated. The same criteria were used when choosing the prime words (for details, see James & Burke, 2000). For the related list, 5 out of the 10 prime words were phonologically related to the target and 5 were not. The 5 phonologically related words shared one or more phonemes with the target word. The remaining 5 unrelated words in this list were matched with the related words with respect to number of syllables, frequency, and stress but did not share any common phonology with the target. For the unrelated list, all 10 words were phonologically unrelated to the target (i.e., they shared no phonemes with the target). Each participant was given either the unrelated or the related list. All participants had to fill in a questionnaire to provide information on how much caffeine they consumed per day (Amendola, Gabrieli, & Lieberman, 1998).

Caffeine. The participants took either 200 mg of caffeine or a placebo. The caffeine group was given the drug in the form of tablets. Both groups were administered the substance and then given the test 40 min after intake. The study was performed double-blind.

Procedure. A personal computer was used to present stimuli and record responses. To ensure collection of "good" TOTs, the instructions stated that the answer was only on the tip of the tongue if the participants were absolutely sure that they knew the answer to the question but could not retrieve it at that particular moment. The instructions also said that it was not enough for the participants to be able to recognize the word if they were to see it, they had to be sure that sooner or later they would be able to retrieve the word without help.

Following the instructions the first trial began. The 10 prime words appeared on the screen one by one. They were presented for 4 s each, and participants read them aloud and decided after each word how difficult they found it to pronounce. For this, they used a 5-point scale, with *1* being easiest and *5* being hardest. Immediately after the 10th prime word, the general knowledge question appeared on the screen. Participants had to respond within 15 s by pressing Keys 1, 2, or 3, signifying "TOT," "don't know," or "know," respectively. If they were in the TOT state, after they had pressed *1*, the experimenter gave, one at a time, the phonemes of the correct word to check whether the participants were in the TOT state for the correct word. If the participants pressed *2*, a "don't know" response, the next trial began (i.e., the 1st prime word of the set of 10 appeared on the screen). Finally, if the participants thought they knew the answer, after they pressed *3*, they were instructed to type in their answer, which appeared on the screen as they typed. Total time from onset of the 1st prime word to the general knowledge question was 40 s, which was in keeping with the time scale for STP as reported by Anwyl et al. (1988). The experiment was carried out in Italian.

Results

Table 1 shows the detailed results of responses for all subgroups. Figure 3 shows the number of TOT correct responses over the four subgroups.

An analysis of variance (ANOVA) was performed on these data. There was a significant interaction effect, $F(1, 60) = 15.99$, $p < .01$, for Drug × List over all participants.

As can be seen from Figure 3, a significant positive priming effect of the related list was found for the caffeine subgroup. For this subgroup, significantly fewer correct TOTs were seen when primed with the related list than when primed with the unrelated, $F(1, 30) = 20.28$, $p < .01$. We saw an opposite effect for the placebo subgroup, in which priming with the related list induced more TOT corrects than did priming with the unrelated list, $F(1, 30) = 2.92$, $p < .05$.

For the related list, there was a significant decrease in the number of correct TOTs for the caffeine subgroup compared with the placebo subgroup, $F(1, 30) = 6.33$, $p < .01$. In contrast, for the unrelated list, the caffeine subgroup produced significantly more correct TOTs compared with the placebo subgroup, $F(1, 30) = 9.83$, $p < .01$.

Discussion

The significant interaction effect ($p < .01$) of Drug × List over all participants demonstrates that the effect of drug on list is

Table 1
Mean (±SEM) Numbers of Responses for the Related and Unrelated List for Both Placebo and Caffeine

	Priming type			
	Unrelated		Related	
Type of response	Placebo	Caffeine	Placebo	Caffeine
TOT				
Total	11.69 (1.68)	18.63 (1.50)	15.94 (1.77)	9.25 (0.98)
Correct	8.00 (1.27)	13.31 (1.12)	11.31 (1.46)	7.31 (0.80)
Know				
Total	56.25 (2.63)	51.44 (3.02)	55.94 (2.58)	61.88 (3.08)
Correct	36.69 (2.36)	33.19 (2.34)	36.69 (2.22)	45.25 (2.91)
Don't know	32.06 (2.67)	29.88 (2.73)	28.13 (2.06)	28.81 (2.95)

Note. Values are for 64 participants. The sample sizes for each group were related placebo = 16, related caffeine = 16, unrelated placebo = 16, and unrelated caffeine = 16. Tip-of-the-tongue (TOT) correct responses are classified as any TOT response that was subsequently verified as being for the target word and not for a different answer.

significantly different across lists. The significant *decrease* in TOT corrects for the caffeine subgroup on the related list compared with the placebo group (*M*s = 7.31 vs. 11.31, $p < .01$) shows a significant phonological priming effect for participants who had taken caffeine. The significant *increase* ($p < .01$) in TOT correct (i.e., a blocking effect for the caffeine subgroup when presented with the unrelated list) can be explained by an interference effect by enhanced STP within the phonological retrieval system. This transiently increases the likelihood of recalling the primed "incorrect" phonemes. These contrasting effects for the caffeine subgroup caused solely by manipulation of the phonological primes demonstrates that the effect is likely to be localized to the phonological system and is not a result of the effect of caffeine working on other neural systems involved in the task.

Although the results for the caffeine subgroup do support the hypothesis of an increased STP effect in the phonological retrieval system, the results for the placebo subgroups cannot be accounted for by the priming hypothesis alone, as they are showing the opposite, an increase in TOT correct (mean unrelated placebo = 8.0, mean related placebo = 11.3; $p < .05$) when primed with the related list. This result was surprising because it differs from those of James and Burke (2000), in which a positive priming effect was seen for related words. However, this effect is similar to those reported by Huber et al. (2001). This result is intriguing, as it is not appropriate to speak about an enhancement of a priming effect (with caffeine) if there is no priming effect in the first place. The results for all groups do support the caffeine enhanced STP priming hypothesis, given a weak positive priming effect masked by a dominant blocking mechanism in placebo conditions. However, they do not rule out the possibility that caffeine interacts differently with the unrelated list compared with the related list. To investigate these issues further, we carried out a second experiment in which there was no unrelated list, but participants were given 10 prime words, of which 2 or 3 were related to the target and 7 or 8 were unrelated, or else 7 or 8 words were related and 2 or 3 were unrelated. This allows a more precise functional relationship concerning the effects of related priming on the number of induced TOTs for both the caffeine and placebo conditions.

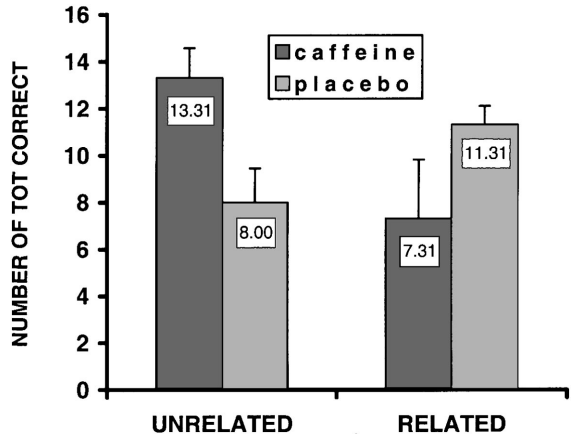

Figure 3. Mean (±*SEM*) number of correct tip-of-the-tongue (TOT) states for each group. Results are for 64 participants divided into four groups. Numbers within the bars represent the mean numbers of TOT corrects.

Experiment 2

In Experiment 2, again two lists of 10 words were compiled to prime 100 general knowledge questions. One list had either 2 or 3 prime words phonologically related to the target and 7 or 8 prime words phonologically unrelated (we call this the 2.5 related list) and the other list had either 7 or 8 prime words related and either 2 or 3 prime words unrelated (the 7.5 related list). If, in Experiment 1, the caffeine subgroup shows a positive priming effect because of the related primes rather than a negative effect with the unrelated primes, then for the caffeine subgroup, the 2.5 related list should yield fewer TOT corrects than it does for the unrelated list in Experiment 1. It should also yield *more* TOT corrects than the 7.5 related list and the related list of Experiment 1 (which was made up of 5 phonologically related words and 5 phonologically unrelated words). Furthermore the caffeine subgroup primed with the

7.5 related list should produce the fewest number of TOT corrects overall.

Method

Participants. Thirty-two native Italian speakers took part in the experiment. They were on average 23.0 ($SE = 0.2$) years old and had 16.0 ($SE = 0.1$) years of education. As in Experiment 1, smokers were excluded, as were people who consumed more than 400 mg of caffeine per day. Women who were pregnant or taking contraceptive pills were also excluded. Participants abstained from alcohol for 24 hr and from caffeine for 12 hr prior to testing. None had participated in Experiment 1.

Ethics. Ethics approval was granted by the SISSA Ethics Committee, and the participants were paid for their contribution.

Materials. The same 100 general knowledge questions used for Experiment 1 were given, and each question was primed with 10 words. For the 2.5 related list, the related lists from Experiment 1 were used; for 50 questions, three related words were replaced with unrelated words, for the other 50 questions, two related words were replaced with unrelated words. For the 7.5 related list, the related list from Experiment 1 was used; for 50 questions, three unrelated words were replaced with related words, for the other 50, two unrelated words were replaced with related words. Again, all words in the lists were matched for number of syllables, frequency, and stress. Each participant was given either the 2.5 related list or the 7.5 related list. There was no condition in which all 10 prime words were related, as we wanted to maintain the hidden nature of the priming, avoiding strategic effects.

Procedure. Caffeine administration and the procedure were the same as in Experiment 1. See previous text for details.

Results

The main results are presented in Table 2. For reference, in Figure 4 we also include the results from Experiment 1. The unrelated list from Experiment 1 is now referred to as 0 related (0 related priming) and the related list from Experiment 1 is referred to as 5 related (5 out of 10 prime words related). Therefore we have four comparison groups: 0 related, 2.5 related, 5 related, and 7.5 related.

We applied a general linear model to the data (which now consist of Experiment 1 and Experiment 2 combined) with drug as a factor (caffeine vs. placebo) and number of related primes as a covariate and also included a Drug × List interaction in the design. There was a significant interaction effect of Drug × List, $F(1, 92) = 34.89$, $p < .01$. For each independent drug group, a linear relationship was found between the number of related primes and the number of TOT corrects (see Figure 4). The line of best fit, calculated using the least mean-square errors, for placebo group yielded gradient $B = 0.68$, $F(1, 46) = 7.98$, $p < .01$, y-axis intercept = 7.75, with regression coefficient $r = .99$, $p < .01$. For the caffeine subgroup, a gradient of $B = -1.05$, $F(1, 46) = 35.49$, $p < .01$, y-axis intercept = −1.06 was found with $r = -.95$, $p < .05$.

Discussion

These results show that the effect of caffeine on the number of TOT corrects is an increasing function of the number of phonologically related prime words. The effect conclusively demonstrates that it is a positive effect of the caffeine plus related priming and not a negative effect of caffeine and unrelated priming. This supports the hypothesis that caffeine is strengthening an STP effect. This is seen as a reduction of TOT corrects when priming is phonologically related to the target and hence aids retrieval and as an active interference when primes are phonologically unrelated to the target because of the enhanced STP strengthening the "wrong" phonemes. This second experiment specifically controlled the amount of related priming. The number of TOT corrects for the caffeine subgroup decreased proportionally to the amount of related phonological priming, whereas for the placebo group, it increases proportionally to the number of related words. These results allow us to conclude that the positive priming results for the caffeine subgroup seen in Experiment 1 were the result of related phonological priming. The clear linear relationship between phonologically related primes and TOTs allows the interpretation of the greater number of TOTs in 0 related caffeine conditions compared with the baseline 0 related placebo conditions to be accounted for as a continuation of the interaction of caffeine and the prime words. It can be clearly seen that the greater number of TOTs for the 0 related caffeine condition can be parsimoniously accounted for by caffeine enhancing the probability of recalling unrelated phonemes during word retrieval. This supports the main hypothesis that the positive priming effects on TOTs can be

Table 2
Mean (±SEM) Numbers of Responses for the 2.5 Related and 7.5 Related List of Experiment 2, for Both Placebo and Caffeine

	Priming type			
	2.5 Related		7.5 Related	
Type of response	Placebo	Caffeine	Placebo	Caffeine
TOT				
Total	12.25 (1.98)	10.38 (1.30)	17.75 (1.00)	7.25 (1.40)
Correct	9.00 (0.38)	8.00 (0.85)	12.88 (0.81)	4.75 (0.88)
Know				
Total	49.88 (3.07)	54.25 (2.66)	42.38 (2.63)	48.63 (2.78)
Correct	30.00 (1.86)	37.75 (1.41)	30.25 (1.24)	32.88 (2.86)
Don't know	37.88 (3.19)	35.25 (3.59)	39.88 (2.47)	44.13 (3.54)

Note. Values are for 32 participants. The sample sizes for each group were related placebo = 8, related caffeine = 8, unrelated placebo = 8, and unrelated caffeine = 8. TOT = tip of the tongue.

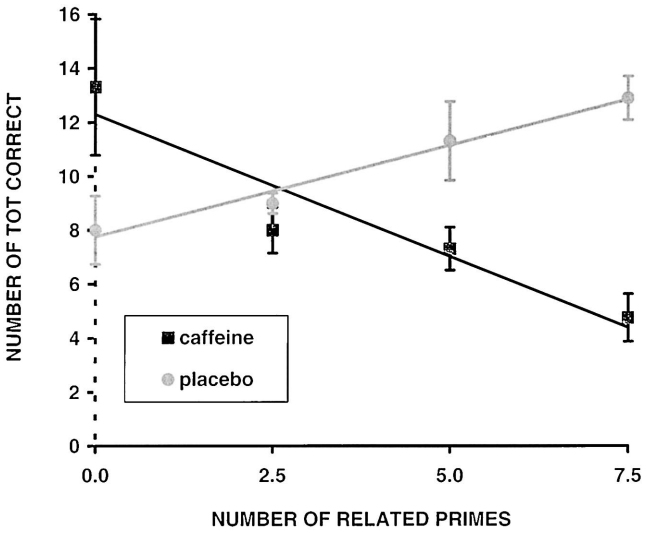

Figure 4. Figure shows the results for correct tip-of-the-tongue (TOT) states for caffeine and placebo groups for increasing number of phonologically related prime words out of a total of 10 primes. Error bars depict standard errors of the mean. Trendlines show best fit linear models for each drug group.

accounted for by STP effects increasing neural activity enhanced by caffeine. The results of Experiment 2 for placebo conditions, namely the existence of the linearly increasing relationship between the relatedness of prime words and TOTs, provide additional support to the results found in Experiment 1 for placebo conditions (i.e., the apparent interference effect of related priming that contrasts with the reported results of James and Burke [2000]).

General Discussion

Our principal hypothesis was that the effect of phonological priming on TOTs could be explained by augmentation and PTP of pyramidal cells in a functionally discrete neuronal system. Additionally, we proposed that the 200 mg of caffeine given to the participants would produce an enhancement of augmentation and PTP. The results obtained using this psychopharmacological paradigm show that, in principle, a priming effect reducing the number of correct TOTs could potentially be accounted for by the cellular mechanisms of augmentation and PTP working in a functionally modular neuronal network.

As seen from the results of both Experiment 1 and 2, the caffeine subgroup showed a strong priming effect as a function of the number of primes phonologically related to the target. Furthermore, when prime words were unrelated there was an obvious interference effect, suggesting that caffeine is strengthening "incorrect" primes actively interfering with word retrieval. Thus, results for both the related and unrelated conditions can be predominantly accounted for by the single hypothesis that caffeine is enhancing an augmentation and PTP effect in neurons of the phonological retrieval system.

The results from the placebo subgroup are consistent with the results seen in previous priming studies when the prime–target interval is long. There are several studies showing that when the prime–target interval is short there is a facilitation effect, hypothesized to be the result of neural persistence—lasting activation of the prime—for related stimuli (for details, see Huber & O'Reilly, 2003) and when the time interval is increased, neural accommodation becomes apparent. The time period that we are interested in here, from the first prime until the general knowledge question appears, is 40 s, assumed to be a long duration. Therefore it is not unreasonable to assume that in placebo conditions the neurons are undergoing neural accommodation, whereas caffeine affects mechanisms central to the neural persistence. Huber and O'Reilly (2003) suggested that synaptic depression could be responsible for the accommodation seen for long prime durations. Other neuronal adaptation mechanisms exist that are also consistent with the results found here for placebo conditions and those of Huber et al. (2001). One mechanism that may account for the effect seen comes from the Ca^{2+}-activated-K^{+} currents that are known to play a role in controlling afterhyperpolarization (AHP) in neurons (Wang, 1998). An effect of increasing AHP in active pyramidal cells is the transient reduction of the net response of cells that have recently been active. One consequence of this is a relative reduction in the mean firing rate of the recently active neurons. This effect is an increasing function of previous activity and decays over time.

In either case, activating the ensemble of cells responsible for encoding the phonemes of the target word should have the effect of making subsequent attempts to retrieve representations of those phonemes less likely. In the controlled conditions in which the participants carried out the test (i.e., for the placebo subgroup, we ensured the absence of caffeine), any augmentation and PTP that may have occurred was dominated by this baseline negative effect. However, for the caffeine subgroup, the well-studied competitive agonism between caffeine and adenosine A_1 receptors produces increased activity levels enhancing the augmentation and PTP sufficiently to generate a detectable priming effect.

It is true that in the placebo condition we do not see the priming results reported by James and Burke (2000). However it is not stated whether they controlled for caffeine users. By looking at the strong significant effect for the caffeine group and the fact that we do get James and Burke's priming effect for the 5 related-word list (the number of related primes used by James and Burke) when it is averaged over the two drug groups (our mean and standard errors of TOT for the correct word are related = 9.2 [0.90] and unrelated = 10.7 [0.96]), although not significant, $F(1, 62) = 1.2$, $p = .14$, it is plausible to account for their results by supposing that some of their participants had caffeine in their system while carrying out the experiment. It should be noted that the 200 mg of caffeine given to our participants is about the same as that found in two cups of coffee.

We did not set out to explicitly investigate the possibility that modulation of cell response properties could account for results previously attributed to network-based working memory. However, these results suggest that augmentation and PTP may be important in some working memory tasks.

Our account of caffeine's effects is based on the competitive agonism of adenosine at A_1 receptors. We have not considered the possible consequences of caffeine's effects at the A_{2a} receptors. This is the only other mechanism by which caffeine is thought to produce active effects at the concentrations of caffeine relevant here. This in part reflects the fact that the functional impact of the action of caffeine at these receptors is less-well understood (Fredholm et al., 1999). Therefore, our results do not rule out a different

explanation of the cause should the A_{2a} pathway play both a prominent and functionally distinct role from the adenosine agonism of caffeine at the A_1 receptors.

Furthermore, it might be useful for cognitive psychologists to consider the possible effects of caffeine on participants, as caffeine consumption did strongly affect the number of TOTs.

Our methodology has combined psycholinguistic experimentation with a pharmacological manipulation to investigate the neural mechanisms underlying phonological retrieval. The experimental data are consistent with the predictions made by the single assumption that phoneme-specific excitation is enhanced by caffeine, which in turn leads to an enhancement of STP correlated with the primed phonemes. However, the results do not conclusively prove that the underlying neurobiological mechanisms causing the effects have been identified. Any other explanation will have to account for a linearly increasing positive priming effect in caffeine conditions when cued with correlated input as compared to placebo conditions, with a concurrent interference effect when primed solely with uncorrelated stimuli. Further, a linearly increasing effect in placebo conditions must also be explained. In particular, one alternative hypothesis consistent with the results reported here, namely that caffeine simply prolongs "neural persistence," which was identified by Huber and O'Reilly (2003), seems unlikely because such a striking effect of caffeine on neuronal behavior would be strongly evident in many common cognitive tasks. Although the conclusions made about the neurobiology from the results of the cognitive paradigm remain speculative, using the results obtained, we have attempted to correlate psychological data with underlying neurobiological mechanisms.

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Correction to Lindquist and Brown (2004)

The article "Temporal Encoding in Fear Conditioning Revealed Through Associative Reflex Facilitation," by Derick H. Lindquist and Thomas H. Brown (*Behavioral Neuroscience,* 2004, Vol. 118, No. 2, pp. 395–402), contained errors.

On page 396, second paragraph, the sentence beginning on line 6 should read as follows: "Having a stable baseline is critical for studies of reflex facilitation because the experimental designs invariably entail repetitive CR testing, if only to achieve reasonable statistical power (see Choi et al., 2001b; Lindquist & Brown, 2004)."

On page 400, the first heading should read as follows: "*Comparison of New and Old Reflex Facilitation Procedures*"

On page 400, the first sentence under the abovementioned heading should read as follows: "We decided not to use the original measure of reflex facilitation, developed by J. S. Brown et al. (1951), because it suffers from severe interpretational limitations, elaborated in detail elsewhere (Choi et al., 2001b; Leaton & Cranney, 1990; Lindquist & Brown, 2004)."