generates a model structure for the new sequence based on the experimentally determined structure, and refines the model sequence using energy minimization and molecular dynamics. Swiss-PDB Viewer was used to generate the Cys-to-Tyr mutant structure, by replacement of the side chain and selection of the lowest energy rotamer. WebLab ViewerLite (www.msi.com/weblab/index.html) was used to manipulate the resulting models and prepare images for presentation.

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24. We would like to thank D. Hilgemann, R. Lin, and D. Smith for critical comments on the manuscript, A. Chiang for assistance in screening for *exp-2(sa26)* revertants, and A. Fire, J. Ahnn, G. Seydoux, and S. Xu for the gift of pPD95.77. Some strains were received from the *Caenorhabditis* Genetics Center, which is funded by the NIH National Center for Research Resources. J. Thomas kindly provided us with the *exp-2(sa26)* allele. Supported by NIH grants HL46154 to L.A. and NS28407 to R.H.J.

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# Inattentional Blindness Versus Inattentional Amnesia for Fixated But Ignored Words

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**People often are unable to report the content of ignored information, but it is unknown whether this reflects a complete failure to perceive it (inattentional blindness) or merely that it is rapidly forgotten (inattentional amnesia). Here functional imaging is used to address this issue by measuring brain activity for unattended words. When attention is fully engaged with other material, the brain no longer differentiates between meaningful words and random letters, even when they are looked at directly. These results demonstrate true inattentional blindness for words and show that visual recognition wholly depends on attention even for highly familiar and meaningful stimuli at the center of gaze.**

The extent of processing for unattended objects has been debated for over four decades (*1*). Recognition of unattended words is considered a crucial test case (*1–3*), because for these visual stimuli the processing of higher order cognitive properties (such as identity and meaning) can be dissociated from mere visual appearance. Early findings of little awareness or memory for ignored words (*4*) were taken to support the hypothesis that word recognition depends on attention. However, other studies suggested that word recognition still may take place unconsciously or implicitly for ignored words (*5, 6*), which led to proposals that word recognition is fully automatic (*2, 7*).

Functional imaging provides a way to measure unattended processing, but until now it has not been applied to the classic issue of the level of processing for unattended words. Recent data show that attention can modulate the activity evoked by visual stimuli within early brain areas (*8*), but all the stimuli used were meaningless or unfamiliar (for example, flashes, colored grids, or moving dots) and so cannot resolve the issue of unattended processing for meaningful familiar stimuli such as ignored words. Moreover, existing brain imaging data suggest that unattended processing may be attenuated rather than completely eliminated at early levels of processing, so processing of an unattended stimulus still may proceed through to higher levels beyond a rudimentary analysis of physical features (*9*). Here we resolve these issues by showing that brain activity in response to familiar visual words, versus random letters, wholly depends on attention.

We created a situation in which people could look directly at a word without attending to it (*10*). Brain activity was measured with functional magnetic resonance imaging (fMRI) (*11*) as participants viewed displays of a rapid stream of letter strings superimposed on a rapid stream of pictures (Fig. 1). The letter stream either consisted of meaningless strings of random consonants or contained a high proportion of meaningful familiar words. At any one time, participants attended only the stream of letters or only the superimposed stream of pictures in order to detect any immediate repetition of a stimulus within the attended stream. We arranged the stimulus parameters so that monitoring one stream for repetition was sufficiently demanding to preclude any attention to the other stream (*10*), even though both were superimposed at fixation. When the stream of letters was attended, we expected meaningful words within it to activate the extensive left-hemisphere network identified in previous imaging studies of word processing (*12*). The new question was whether meaningful words would similarly produce differential brain activation when the letter strings were ignored, with the superimposed pictures being attended instead. If true inattentional blindness can arise for ignored words, then activation for words versus nonwords should no longer be found. By contrast, if word processing is fully automatic, as is often argued to be the case (*2, 7, 13*), then differential activation still should be found even for ignored words because they are automatically perceived, with any effects of inattention being more akin to inattentional amnesia (*14*) than to inattentional blindness (*15*).

Immediately after scanning, participants underwent surprise recognition memory tests for the meaningful words they had been shown (*16*). Although recognition memory was excellent for those words that appeared in an attended stream, ignored words were not distinguished from new words (Fig. 1, bottom). This confirms that our manipulation of attention was psychologically effective and agrees with previous findings that people cannot recognize the identity of unattended stimuli retrospectively (*17*).

First we compared brain activations when participants were attending to the picture streams versus the letter streams overall (*18*). The stimuli were identical for these comparisons, as were the motor responses when detecting repetition, so any differential brain response must be due to what was attended. Attending to pictures compared with letter strings activated an extensive network of ventral visual areas bilaterally (Fig. 2A, green), whereas attending to letter strings compared with pictures activated a left occipital region (Fig. 2A, red) previously associated with letter perception (*19*). These activations indicate that covert attention can substantially affect neural responses in the visual system even when attended and ignored stimuli are spatially superimposed.

The crucial test for brain responses to meaningful familiar words compares the activation evoked by words versus consonants within the letter stream. When the letter stream was attended, words minus consonants revealed strong activity in a left-lateralized network of areas, including posterior basal temporal, parietal, and prefrontal cortex (Fig. 2B and Table 1). This is consistent with previous lesion and functional imaging studies of word processing (*12, 13, 20*). Because words differ from consonant strings in several respects (for example, legal orthography and phonology, lexical status, semantics), the

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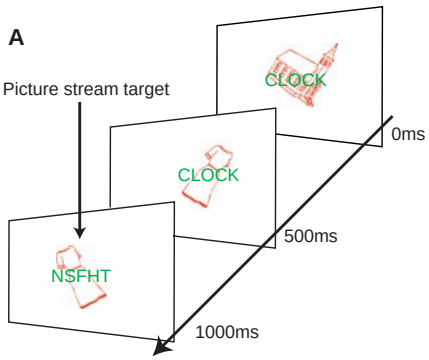
activations may involve all the corresponding word-related processes. Note that word-related activations were found here for attended letter streams, even though our repetition-detection task did not require participants to treat words any differently from nonwords. In this respect, our results agree with previous imaging studies that similarly found word-related activations even in nonlexical tasks (*13*).

Those studies argued on that basis that word processing takes place automatically, as many psychological accounts have proposed (*2, 7, 21*). However, these data argue against fully automatic word processing for the new situation in which the letter streams were unattended, with the pictures being attended instead. The critical interaction between which stream was attended and whether words were presented (that is, testing for a larger effect of words minus consonants when the letter stream was attended) revealed robust left-hemisphere activations virtually identical to those for the simple effect of words when attended (Fig. 2, C and B). Moreover, comparing the same stimuli as before (that is, meaningful words minus consonant strings), but with the letter stream unattended, did not activate a single voxel in these cortical areas, neither in the group analysis (*18*) nor in further analyses of individual participants at low threshold (*22*). The time-course data for attended words versus conso-



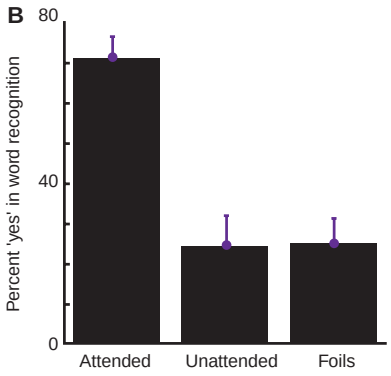




**Fig. 1.** (**A**) Schematic illustration of stimulus configuration [see (*10*) for details]. (**B**) Performance in the surprise recognition memory test for words [see (*16*) for procedure]. Bar graph shows interparticipant mean and standard deviation of percent "yes" responses when judging whether a word had been shown in the imaging part of the experiment. Attended and unattended words refer to physically equivalent displays but with attention directed to the letter stream and to the picture stream, respectively. Foils refer to words that were never presented to a particular participant before, thus providing a measure of the tendency to answer falsely in the affirmative. Participants recognized almost all the attended words but did not differentiate unattended words from foils they had never seen before.

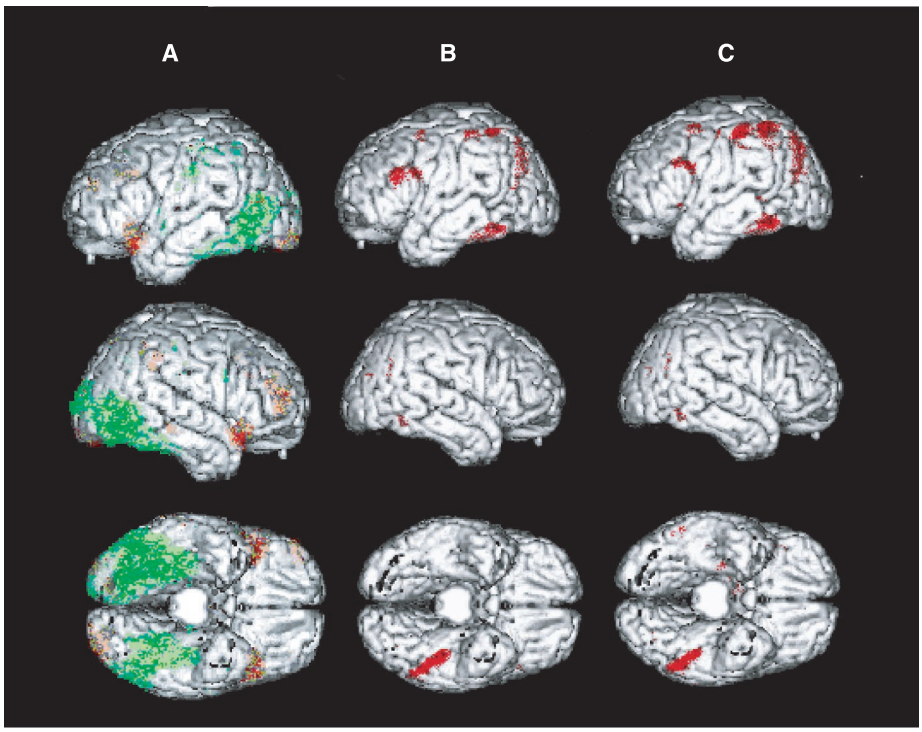



**Fig. 2.** (**A**) Effects of attention on fMRI activity. Three views of a T1-weighted anatomical template in Talairach space, on which are superimposed areas where attention to the picture stream produced significant activation compared with all letter streams (green) or vice versa (attend letter streams minus picture stream; red). (**B**) Simple effect of words compared with consonants when attending letters. Three anatomical views, on which are superimposed in red those areas where words minus consonants produced significant activation when attention was directed to the letter stream (see also left half of Table 1). (**C**) Interaction between attention and word processing. Three anatomical views on which those areas where evoked activity specifically reflected the critical interaction between attention and word identity (where the effect of words minus consonants was greater during attention to the letter streams than during attention to the picture stream) are superimposed in red.

**Table 1.** Coordinates and *z* scores for activation related to word processing. Shown are loci with higher activity for words versus consonants when attention was directed to the letter stream (left columns) and loci where such word-related activity was greater during attention to the letter stream than during attention to the picture stream (right columns). Coordinates shown are for the maxima within each area of activation ($P < 0.05$; corrected for multiple comparisons except where a different corrected value is specifically indicated).

| Cortical region | Attended words minus consonants | | | | Interaction of words and attention | | | |
|---|---|---|---|---|---|---|---|---|
| | Talairach coordinates (mm) | | | *z* score | Talairach coordinates (mm) | | | *z* score |
| Left inferior frontal (BA44) | −39 | 6 | 27 | 4.70 ($P = 0.09$) | −39 | 6 | 27 | 4.41 |
| Left posterior temporal (BA37) | −39 | −36 | −24 | 4.63 | −51 | −51 | −18 | 5.71 |
| | | | | | −42 | −39 | −24 | 4.85 |
| Left posterior parietal (BA7/40) | −33 | −33 | 57 | 4.59 | −33 | −33 | 57 | 5.36 |
| | −27 | −72 | 33 | 4.49 ($P = 0.06$) | −24 | −75 | 42 | 6.50 |
| | | | | | −30 | −57 | 39 | 5.57 |
| Right posterior parietal (BA7) | 36 | −63 | 24 | 4.23 ($P = 0.17$) | 36 | −60 | 33 | 5.32 |

nants and for unattended words versus consonants are shown in Fig. 3. Note that there is no tendency for a stronger response to words than consonants when the letter stream is unattended (*23*).

These functional imaging data show that word processing can strongly depend on attention, contrary to previous claims in both psychology (*2, 21*) and functional imaging (*13*) for full automaticity. The data suggest that word processing is not merely modulated but is abolished when attention is fully withdrawn. If unattended words suffered only from inattentional amnesia (*14*), a differential response to words versus consonant strings should have been found at the time they were presented even when unattended because of automatic processing. By contrast, if ignored words suffer true inattentional blindness, the differential response that is observed for words when attended should be completely eliminated when they are unattended. Our results support the latter prediction. When covert attention was directed to other material for a demanding task, even words presented directly at the fovea produced no detectable differential cortical activity whatsoever (Fig. 3). Differential activation for words compared with consonants was seen neither in classic language areas nor in any area of visual cortex when unattended (*18, 22*).

The posterior basal temporal activation (see Fig. 2B) found for attended words has been observed in previous imaging studies of word processing (*13, 22*). Lesions to this area can produce alexia or visual anomia (*24*). A recent study showed that words activate this area not only in sighted readers but also in blind Braille readers, which suggests that it is an important association area for high-level representation of word identity (*20*). These data extend previous findings by showing that word-related activation of this area critically depends on attention. Its previous activation during implicit reading tasks, with no lexical response required, was interpreted as showing fully automatic word processing (*13*). However, unlike this experiment, those studies presented individual words in total isolation, for up to 1 s, so the lexical properties of the stimulus were unlikely to be ignored. Our study shows that the basal temporal activation for words can be eliminated under conditions of true inattention.

The activations for attended words in left prefrontal cortex (Fig. 2B), close to Broca's area, have also been observed in previous imaging studies of word processing (*12*), where a role for this area in phonological retrieval and semantics was suggested. We also found activations for attended words in several areas of left parietal cortex and a homologous area on the right. Enhanced activity in left parietal cortex for words has previously been associated with orthographic to phonological conversion and with word meaning in a distributed semantic system (*25*). Again, our data suggest that such activity may be obliterated under conditions of full inattention.

Our imaging results imply true inattentional blindness for ignored words in the following sense. We do not suggest that our participants were blind to the presence of letters (*26*) when they were attending the superimposed pictures, but rather they were blind to those properties that distinguish words from random strings of consonants. The phenomenal experience when performing the task is indeed of knowing that both a (red) picture and a (green) letter string are present concurrently in the two rapid streams but being aware of the identity of each item only for the attended stream. The functional imaging data accord with this phenomenology. The success of our method may lie in the taxing demands of the picture task establishing conditions of full inattention for the words (*27*). Under conditions that do not fully engage attention, incidental processing of linguistic properties may take place even during nonlexical tasks. Indeed, as in previous studies of word processing, which presented letter strings in total isolation (*13*), words in the attended stream produced lexical activations here despite the nonlexical nature of our repetition task. These activations were eliminated only when the picture stream was being attended instead and the words were ignored. Although unattended words might be processed to a greater extent under conditions that impose a lower load than the present demanding picture task (*28*) or that use only a single stream of stimuli (*29*), our results suggest that, under the appropriate conditions of true inattention, words can be directly fixated but not read.

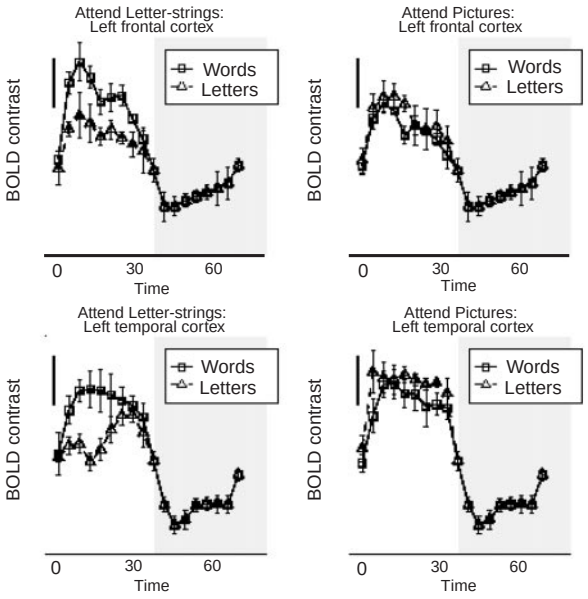



**Fig. 3.** Time course of foci of activity in left frontal (upper) and left posterior basal temporal cortex (lower). All four panels use the same plotting conventions. Average BOLD contrast evoked at each locus (see Table 1 for coordinates) is plotted as a function of time, collapsing across epochs and participants. Note that the areas whose time courses are shown were identified as those areas showing a maximal simple main effect of words under attention to letters. Unshaded areas represent scans acquired in the experimental conditions [see (*10*) and (*11*)] and shaded areas represent those acquired during the passive fixation baseline. Error bars indicate interparticipant standard error and dark scale bar represents 0.5% BOLD signal change. Activity evoked when the letter stream contained meaningful words is plotted with black squares and a solid line, and activity when the same stream included only meaningless letter strings is plotted with triangles and a dotted line.

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10. Six right-handed participants (two male and four female; 23 to 29 years old) gave informed consent to participate. Displays like those in Fig. 1 were presented every 500 ms for 250 ms. All pictures belonged to the Snodgrass-Vanderwart set [J. G. Snodgrass and M. Vanderwart, *J. Exp. Psychol. Hum. Learn. Mem.* **6**, 174 (1980)]. Superimposed on the pictures were strings of five letters, comprising either random consonants or high-frequency concrete nouns. Total stimulus size was about 5°, centered at fixation. In different scanning epochs, the letter stream included either letter strings alone or 60% concrete nouns mixed with letter strings. When words were present, they were introduced only after the first eight items, as previous work has shown that people notice distractors more at the beginning of a stream [A. M. Treisman, R. Squire, J. Green, *Mem. Cogn.* **2**, 641 (1974)]. Participants performed a single task while they underwent brain imaging (*11*), detecting immediate repetitions of stimuli within whichever stream

(letters or pictures) they attended. This task was performed for epochs of 36.9 s with repetition targets occurring pseudorandomly every six stimuli on average. To ensure that attending pictures was demanding, pictures had different orientations within any repeated pair, rotated 30° clockwise or counterclockwise from their natural axis (Fig. 1). Repetitions also took place in the unattended stream (requiring no response), uncorrelated in time with repetition in the attended stream. A button press response was required with auditory feedback for hits and misses. Participants were instructed about which stream to attend by an auditory cue in the rest epoch preceding each task epoch. The number of targets per epoch was balanced across conditions. Task order followed a within-participant Latin-square design. During both attention to letter strings and attention to pictures, any words were drawn from one of two different lists balanced for word frequency, concreteness, and imageability and were fully counterbalanced across participants.

11. A Siemens VISION (Siemens, Erlangen) acquired blood oxygenation level–dependent (BOLD) contrast functional images at 2 T. Image volumes were acquired continuously every 4100 ms, each comprising 48 contiguous 3-mm-thick slices to give whole-brain coverage with an in-plane resolution of 3 mm by 3 mm. Functional imaging was performed in four scanning runs comprising 288 volumes in total. In each scanning run, after eight image volumes were discarded to allow for T1 equilibration effects, the experimental conditions were presented for 36.9 s (nine scans) alternating with fixation control (rest) for nine scans. Condition order was counterbalanced across participants.
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16. After scanning, a surprise recognition memory test was presented. Participants indicated by button press whether each word shown had been presented during the scanning experiment. Three randomly intermingled word lists were tested (attended words, unattended words, and never-seen foils), matched for word frequency, concreteness, and imageability, with list membership counterbalanced across participants. Memory for attended words was better than for unattended words ($t = 5.2$, $P < 0.05$) and the latter did not differ from the chance rate given by false-positive responses to never-seen foils ($t = 0.08$, $P > 0.5$).
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18. Statistical parametric mapping software (SPM 99, http://www.fil.ion.ucl.ac.uk/spm) was used. The imaging time series was realigned, spatially normalized to stereotactic Talairach space, and smoothed with a Gaussian kernel of 10 mm full-width at half-maximum. Voxels activated during the experimental conditions were identified by a statistical model containing four delayed boxcar waveforms that represented the mean activity evoked in the experimental conditions. High-pass filtering removed participant-specific low-frequency drifts in signal, and global changes were removed by proportional scaling. Each component of the model served as a regressor in a multiple regression analysis. Masking with the contrast between the four experimental conditions versus baseline fixation was used to restrict our analysis to areas activated by the experimental conditions. A statistical threshold of $P < 0.05$, corrected for multiple comparisons, was used except where specified. Further inspection of any simple effect of unattended words minus consonants lowered the threshold to uncorrected $P < 0.001$ but still found no activation.
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22. Spatial variability among activations across subjects might obscure an otherwise consistent neural response to ignored words. To test this, we repeated the analysis, but with the voxel of peak activation to attended words selected within individual subjects (for all the cortical areas in Table 1, within a 10-mm radius of the group activation coordinates) to identify any activation to unattended words. Again, we found no significant differential activation (all $P < 0.05$).
23. The numerically lower activity for unattended words versus unattended consonants in Fig. 3 raises the possibility that inhibitory mechanisms might suppress responses to unattended words [possibly related to the psychological phenomenon of negative priming (*6*)]. However, the apparent lowering of activity was not reliable; our data showed neither significant activation nor deactivation for unattended words in these cortical areas. Moreover, psychologically, negative priming is typically eliminated under conditions of high attentional load [N. Lavie and E. Fox, *J. Exp. Psychol. Hum. Percept. Perform.*, in press; A. Treisman and B. DeSchepper, in *Attention & Performance XVI*, T. Inui and J. L. McClelland, Eds. (MIT Press, Cambridge, MA, 1996), pp. 15–46] such as the present demanding picture task.
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30. Supported by the Wellcome Trust and by an Economic and Social Research Council (U.K.) grant to J. D. We thank F. Crick, R. Frackowiak, C. Koch, and C. Mummery for helpful comments and the late I. Rock for inspiration.

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# Pharmacological Rescue of Mutant p53 Conformation and Function

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**Compounds that stabilize the DNA binding domain of p53 in the active conformation were identified. These small synthetic molecules not only promoted the stability of wild-type p53 but also allowed mutant p53 to maintain an active conformation. A prototype compound caused the accumulation of conformationally active p53 in cells with mutant p53, enabling it to activate transcription and to slow tumor growth in mice. With further work aimed at improving potency, this class of compounds may be developed into anticancer drugs of broad utility.**

The p53 tumor suppressor gene is mutated with high frequency in human cancers, and reintroduction of wild-type p53 can suppress tumorigenicity (*1*). The transcription regulatory and tumor suppressor activity of p53 is absolutely dependent on the ability of the protein to maintain the DNA binding conformation (*2*). A large number of weakly interacting amino acids in the central DNA binding domain (DBD) of p53 contribute to the stability of a structured scaffold that orients the two loops and the loop-sheet-helix motif of the DNA binding surface (*3*). Recent evidence suggests that the most frequently encountered mutations in p53 reduce the thermodynamic stability of the DBD (*4*). Destabilization of the active conformation, which occurs under denaturing conditions or upon mutation of p53, reduces the binding of p53 to specific peptides, to cellular and viral proteins, and to the monoclonal antibody (mAb) mAb1620 (*5*). In contrast, the epitope for mAb240 is exposed when the active conformation is disrupted (*6*).

Ablation of a negative regulatory domain at the p53 COOH-terminus by antibodies and peptides has been used to promote the activity of certain mutant p53 forms (*7*). Here, we present an alternative approach to promoting p53 activity by stabilizing the active conformation of the DBD. We observed that purified wild-type p53 DBD is naturally temperature-sensitive for loss of the active conformation. The epitope for mAb1620 was lost in a temperature- and time-dependent manner when the protein was immobilized on microtiter plates and heated (Fig. 1A). An eight–amino acid epitope tag (FLAG) that was fused to the DBD remained fully stable under these conditions. Furthermore, loss of the 1620 epitope occurred in concert with the enhanced appearance of the 240 epitope, confirming the transition of the protein into a nonfunctional conformation. The half-life of

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