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Internally generated preactivation of single neurons in human medial frontal cortex predicts volition

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Abstract

Understanding how self-initiated behavior is encoded by neuronal circuits in the human brain remains elusive. We recorded the activity of 1019 neurons while twelve subjects performed self-initiated finger movement. We report progressive neuronal recruitment over ~1500 ms before subjects report making the decision to move. We observed progressive increase or decrease in neuronal firing rate, particularly in the supplementary motor area (SMA), as the reported time of decision was approached. A population of 256 SMA neurons is sufficient to predict in single trials the impending decision to move with accuracy greater than 80% already 700 ms prior to subjects' awareness. Furthermore, we predict, with a precision of a few hundred ms, the actual time point of this voluntary decision to move. We implement a computational model whereby volition emerges once a change in internally generated firing rate of neuronal assemblies crosses a threshold.

Volitional control is at the root of our notion of self (Haggard, 2008; Jeannerod, 2007; Laplane et al., 1977). Impairments in the ability to express or detect volitional output can be devastating. Although the nature of voluntary action is a centuries-old question, the study of its neuronal basis is exceedingly difficult as it involves a phenomenon intrinsic to an organism and invisible to an observer. The neuronal circuits and mechanisms underlying self-initiated behavior are poorly understood.

In contrast to reflex actions, cortical function is essential for volitional control of movements (Brass and Haggard, 2008; Desmurget and Sirigu, 2009; Haggard, 2008; Laplane et al., 1977). On the basis of neurological cases, electrical stimulation, scalp electroencephalography, neuroimaging studies and animal neurophysiology, a network of structures in the parietal and premotor cortex has been shown to play a key role in volition. There is substantial evidence implicating the parietal and medial frontal lobes in the representation of intention and in initiation of self generated motor activity. This evidence is

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derived from lesions in animals and in patients (Assal et al., 2007; Brinkman, 1984; Fourneret et al., 2002; Laplane et al., 1977; Sirigu et al., 2004; Sirigu et al., 1999; Thaler et al., 1995), physiological recordings (Haggard and Eimer, 1999; Libet et al., 1983; Shibasaki et al., 1980; Yazawa et al., 2000), magnetoencephalography (Erdler et al., 2000), electrical stimulation in humans (Desmurget et al., 2009; Fried et al., 1991; Lim et al., 1994), and neuroimaging (Farrer et al., 2008; Lau et al., 2004a; Lau et al., 2004b; Milea et al., 2007; Soon et al., 2008). Macaque studies have pinpointed early events in the planning of movement to neuronal populations in supplementary motor area (Pesaran et al., 2008; Romo and Schultz, 1992; Shima and Tanji, 2000; Tanji, 1994) and parietal areas (Andersen and Buneo, 2002; Maimon and Assad, 2006a, b). It has been proposed that areas within parietal cortex (including Brodmann areas 39 and 40) may participate in conscious intentions (Andersen and Buneo, 2002; Assal et al., 2007; Desmurget and Sirigu, 2009; Farrer et al., 2008; Gold and Shadlen, 2007; Haggard, 2008; Sirigu et al., 2004; Sirigu et al., 1999). These areas also receive and process sensory input (Andersen and Buneo, 2002; Gold and Shadlen, 2007) and project directly to premotor cortex (Andersen and Buneo, 2002; Desmurget and Sirigu, 2009). It has been proposed that premotor areas are involved in unconscious internally generated voluntary action (Brass and Haggard, 2008; Desmurget and Sirigu, 2009; Haggard, 2008; Libet et al., 1983).

An intriguing line of research in humans has identified a readiness potential preceding volition (Deecke et al., 1969; Haggard, 2008; Haggard and Eimer, 1999; Libet et al., 1983; Matsuhashi and Hallett, 2008). Scalp EEG and MEG recordings have revealed changes in neural activity preceding awareness of volitional state by hundreds of ms (in some studies even seconds). Additionally, recent imaging studies have identified activity changes in medial prefrontal regions that are predictive of voluntary decisions (Haggard, 2008; Soon et al., 2008). Here we examine the neuronal correlates underlying control of self-initiated movement in humans by using single neuron recordings to address whether neuronal activity is predictive of subjective awareness of human motor behavior on a single trial basis. We take advantage of a rare opportunity to examine the function of the human frontal and temporal lobe at the neuronal level and millisecond temporal resolution while subjects report their subjective intentions. Over an interval of more than 1000 ms *prior to subjects' awareness of the decision or urge to act*, we show that there is a progressive recruitment of neurons that change their firing patterns either in an excitatory or an inhibitory manner. These neurons are predominantly located in the SMA proper, pre-SMA, and anterior cingulate, and their activity correlates with the emergence of self-generated intentions in single trials well before the subject becomes aware of his internal state. We propose a simple quantitative biophysical model for the emergence of self-initiated behavior from the activity of small populations of neurons.

RESULTS

We studied 12 subjects with pharmacologically intractable epilepsy implanted with depth electrodes to localize the focus of seizure onset (Experimental Procedures). The electrode placement was determined exclusively by clinical criteria (Engel et al., 2005). We adopted a paradigm originally described by Libet and colleagues (Libet et al., 1983). Subjects were presented with an analogue clock depicted on a laptop and were instructed to fixate at the center (Fig. 1A). A clock dial rotated on the screen with a period of 2,568 ms. Subjects were instructed to place their right index finger on a key on the laptop keyboard, to wait for at least one complete revolution of the dial, and then press the key whenever "they felt the urge to do so" (3 subjects performed a variant of the task where they could also choose whether to use the right or left index finger). After pressing the key, the clock dial stopped and subjects were asked to indicate where the clock handle had been when they first felt the urge to move. We note that this "urge to move" can be interpreted as a decision for self-initiated

movement. In each trial, we registered the time of key press (P) and the reported onset time of the "urge/decision to move" (W). The distribution of W and P times (Fig. 1B–C) can be approximately fit by an exponential, which is consistent with a constant hazard function (Rausand and Hoyland, 2004) (as opposed to other strategies). There were very few trials in which the subjects pressed a button immediately after the first revolution of the handle (Fig. 1C; S3A). The time between W and P was short and variable from trial to trial (Fig. 1D). The W time reported by the subjects averaged at 193±261 ms (mean±SD) prior to key press (Fig. 1D), similar to previous reports (Haggard and Eimer, 1999; Libet et al., 1983; Matsuhashi and Hallett, 2008). There is a lag of approximately 90 ms (93±35 ms, mean ±STD) between the earliest detectable electromyographic (EMG) signal and the actual key press (Fig. S3C–D).

We recorded the extra-cellular activity from a total of 760 units in the medial frontal lobe (264 single units and 496 multi units; e.g. Fig. 2A–B) while subjects performed the task. Recorded regions include the supplementary and pre-supplementary motor area (SMA, and pre-SMA), and also the rostral and dorsal aspects of the anterior cingulate cortex (ACC) (Fig. 2D, S6 Table 1, and Experimental Procedures). We also recorded from 259 additional units in the temporal lobe (Table 1). The spike trains showed a coefficient of variation that was close to 1, similar to the one expected for a Poisson process and as previously shown for many other cortical neurons (Fig. 2C). A sample of the recordings and the task is shown in Movie S1.

To assess whether or not units changed their firing rate in relation to the reported decision to move (W), we aligned the spike trains in each trial relative to W. Figure 2E depicts the activity of a single neuron in dorsal anterior cingulate cortex while the subject performed 63 trials of the task. This neuron increased its activity only after W, the reported onset of volition; in fact, the clearest change was after key press (green vertical line). A strikingly different pattern is exhibited by a neuron in the pre-SMA (Fig. 2F), recorded simultaneously with the unit depicted in Fig. 2E. This neuron increased its firing rate from a baseline of 4 Hz up to a peak firing rate of 12 Hz. This increase of firing rate commences about 700 ms *before* W, that is, well before the subject becomes aware of the decision/urge to move. In this example, the rise continues beyond the W point and past the key press, before it declines and returns to baseline.

Comparing the neuronal activity prior to W (400 ms interval) with the baseline firing rate (interval from −2500 to −1500 ms with respect to W; Experimental Procedures) we found that 128 out of the 760 neurons in the medial frontal lobe (17%) significantly changed their firing rate (ranksum test, $p<0.01$, Table 1). This proportion is substantially greater compared to only 20 out of 259 (8%) in the temporal lobe ($\chi^2(1)=18.3$, $p < 10^{-4}$; Tables 1, S1–S2). The number of units that showed changes in firing rate with respect to baseline in the frontal lobe was highly significant compared to different possible null hypotheses defined by either creating surrogate spike trains or by randomly shifting W (Fig. S1A). In contrast, the number of units that showed changes in firing rate in the temporal lobe was comparable to the numbers obtained with surrogate spike trains (Fig. S1B). In the medial frontal lobe, these changes were seen both in the SMA (pre-SMA and SMA proper) and in the ACC regions (dorsal and rostral aspects). The number of units that showed changes in firing rate was more than 3 standard deviations from the values expected by chance (and in many cases well above 5 standard deviations) for all four frontal lobe locations (Fig. S1C–F, except for S1C2 and S1D3). The greatest proportion of neurons changing their activity before W (37 out of 163 neurons, 23%) was seen in the SMA proper (Table 1, S2). In addition to the neurons that changed their activity before W, another 98 out of 760 units (13%) in the medial frontal lobe changed their firing rate only after W. Such post-W changes were observed in similar proportions in the temporal lobe (28 units out of 259 (11%); Table 1).

The average PSTHs reveal a gradual change in firing rate (e.g. Fig. 2E–F, 3, 4A–C). Gradual changes in the average PSTH could arise from either gradual changes in individual trials (Fig. S2A) or from abrupt changes in individual trials with variable transition times (Fig. S2B). To quantify the speed of firing rate changes in single trials, we fitted a logistic function to the spike trains after smoothing with a 200 ms Gaussian (Fig. S2C). Upon examining individual trials, we find examples of relatively gradual transitions (e.g. Fig. S2D) and examples of more abrupt transitions (Fig. S2E). The average fitted parameters for all units are shown in Fig. S2F–G revealing a wide range of abrupt/gradual responses in individual trials.

We observed two main patterns of firing changes in medial frontal neurons prior to W (Fig. 3, 4A–C). The first was a *progressive increase* in the average firing rate commencing well before W illustrated by the examples in Fig. 3A–D and I–K ("I units" for *increase* in firing rate). We observed rises beginning several hundreds of ms prior to W (Fig. 3A–C), or sometimes several thousands of ms prior to W (Fig. 3I–K), or rises with a steeper slope commencing closer to the W time point, e.g. ~400 ms prior to W (Fig. 3D). Rises sometimes persisted for several hundreds of ms beyond W (Fig. 3A–B), while in other cases, activity sharply decreased around W or after movement (Fig. 3C–D; 3I–K). The second pattern observed was a *progressive decrease* in the average firing rate with a similar temporal profile commencing several hundreds of ms prior to W ("D units" for *decrease* in firing rate, Fig. 3E–H, L–N). In some cases, changes started several thousands of ms prior to W (Fig. 3L–N). Activity changes reached a plateau at W often near zero firing rate (Fig. 3F,N) or increased at or near W (Fig. 3G,H,M). The average normalized response profile of all medial frontal lobe neurons responding prior to W (Fig. 4A), demonstrates the gradual patterns of average firing rate increase and decrease prior to W. There was no significant difference between the baseline firing rates of "I" and "D" cells: 5.3±4.5 Hz and 5.8±5.5 Hz respectively (mean±S.D.; p=0.3 one tailed two-sample equal variance t-test). These response patterns cannot be attributed to a mere selection bias of "I" units with high firing rates and selection of "D" units with low firing rates in the 400 ms before W (c.f. Fig. S1G vs. Fig. 4A). Interestingly, the population average shows a reversal of the slope of responses just before W (100 to 200 ms) as exemplified by several of the individual examples (Fig. 3C,I,J,K and 3G,H,M). These pre-W patterns were observed both for MUA and SUA (Fig. 4B). These response patterns were observed for the ACC (dorsal and rostral) and pre-SMA and SMA proper (Fig. 4C1–C2). In addition to the changes in mean firing rate we also observed parallel changes in the standard deviation of the firing rate (Fig. 4C3–C4). More details about the anatomical distribution of neurons increasing/decreasing their firing rates prior to W are provided in Table S1.

In parallel to the process of individual medial frontal neurons steadily altering their firing rates, the *number* of recruited neurons that change their activity compared to the baseline period (2500 to 1500 ms before W) also increased as W is approached (Fig. 4D). Of the 760 medial frontal neurons recorded, 55 changed their firing rate relative to baseline already 1000 ms before W, while at the last 400 ms before W, this population increased to 128 neurons. Figure 4E depicts the temporal profile of neuronal recruitment in each of the anatomic regions recorded in the medial frontal lobe, showing greatest and earliest recruitment in the SMA proper.

Several aspects of this task have been subject of intense debate in the field (reviewed in (Desmurget and Sirigu, 2009; Haggard, 2008; Shibasaki and Hallett, 2006); see also (Joordens et al., 2002; Libet, 1985; Trevena and Miller, 2002) and comments therein). We open the discussion to these issues by providing several additional analyses and controls that were not possible before in the absence of single-unit responses. The number of recruited neurons depends on the baseline period. The definition of the baseline in this task has been a

matter of considerable debate in the field. As illustrated by the examples in Fig. 3I–N, some units showed changes in firing rate before the 2500 to 1500 ms baseline period used in Table 1. As we push the baseline period to earlier times, the overall number of trials decreases (subjects rarely waited for more than 3 revolutions of the handle; Fig. 1B–C). Using 5000 to 4000 ms before W as the baseline produces similar results to the ones reported here and reveals that many units show changes in firing rate several thousand ms before W (Fig. S3E). It was not possible to use a baseline earlier than 10,000 ms because of insufficient number of trials (Fig. 1B).

Key to this task is the volitional aspect of motor output; this has also been a matter of debate in the literature. It seems unlikely that subjects were "cued" by the clock handle completing the first revolution. First, as noted in the approximate exponential fits in Fig. 1B–C, the hazard rate was approximately uniform which is indicative of the random variations in trial length (Rausand and Hoyland, 2004). Second, there were very few "cued" trials where subjects responded within 1500 ms of the first revolution of the handle (Fig. S3A). Third, we did not observe any clear difference in the neurophysiological responses between those few trials where P<1500 ms and those trials with P>5000 ms after the first revolution of the clock (Fig. S3B).

The close temporal correlation between W and P (Fig. 1D; S3F–G, S4) makes it difficult to dissociate these two time points. This tight temporal correlation makes sense within this task (there is no reason for subjects to feel the urge to move (W) and wait for a long time before executing the movement (P)). There were very few trials with a long interval between W and P (Fig. 1D) and we did not observe any clear neurophysiological differences between those few trials with P-W>600 ms and those trials with P-W<300 ms (Fig. S3F–G). To further examine whether the onset of neuronal activity changes was related to W and P, we estimated the response onset time in individual trials (Experimental Procedures; Fig. S4A). Figure S4B shows several examples illustrating the tight correlation between W and the onset of firing rate changes in individual units and individual trials. The average correlation coefficient between W and the neuronal response onset time was 0.48±0.45 (mean±SD, median=0.40, range=[−0.32,0.99]); the average correlation coefficient between P and the neuronal response onset time was 0.49±0.42 (mean±SD, median=0.37, range=[−0.28,0.99]) (Fig. S4C).

The subjective nature of W has also been called into question (e.g. (Joordens et al., 2002)). It is likely that there is a considerable degree of inaccuracy in reporting W. In an attempt to bound the inaccuracy in W, we considered two types of timing errors: time shifts and time jitter. To estimate the effect of temporal shifts on the results, we moved W in each trial by a fixed amount ranging from −1600 ms (that is, moving W 1600 ms earlier than the actual reported W) all the way to P (Fig. S4D1) and repeated the previous analyses to compute the number of neurons that show changes in firing rate. We observed that small temporal shifts on the order of ±200 ms would still be compatible with the data. In fact, shifting 50 ms earlier than the reported W actually increased the total number of responsive neurons. We speculate that this could reflect a systematic bias whereby subjects were late in reporting W. However, the results are not compatible with shifts in W of several hundred ms. To estimate the effect of temporal jitter in W, we moved W in each trial by a random amount taken from a Gaussian with zero mean and standard deviations ranging from 25 to 3200 ms (Fig. S4D2). We observed that the number of responsive units would be close to the reported one with temporal jitters <200 ms but the results are not compatible with temporal jitters of several hundred ms. The analyses in Fig. S4D put an approximate temporal bound on the accuracy of W. These results are consistent with the individual histograms showing variability in the peak response with respect to W (Fig. 2E–F, 3).

Figure 5A depicts the activity of 8 selected neurons from one experimental session (out of the 37 available units simultaneously recorded during this session) showing activity changes several hundred ms prior to W. Given the responses observed at the level of individual neurons prior to W, we hypothesized that the decision to perform the movement would depend on the concerted activity of ensembles of neurons such as the ones depicted in Fig. 3 and 5A. Indeed, we could often record simultaneously from several neurons in different brain regions. We therefore asked whether we could decode W in single trials based on the activity of neuronal ensembles. To address this question we used a support vector machine (SVM) classifier (Hung et al., 2005). Given the activity of a population of neurons at a certain time, we first used the classifier to quantify how well we could discriminate activity before W from baseline activity in single trials (Experimental Procedures and Fig. S5A). We started by decoding, on a trial-by-trial basis, the activity of individual neurons recorded during each experimental session. Although the activity of the "best" individual unit in this session, a neuron from right pre-SMA, yielded almost 60% discrimination performance already 500 ms prior to W, the "worst" unit in right anterior cingulate, or the average of all individual units in the population had close to chance performance at this time. We next considered an ensemble of 37 neurons consisting of all the units that were *simultaneously recorded during this experimental session* (Fig. 5B). The population of neurons showed a distinct activity pattern that could be discriminated from baseline in individual trials better than chance well before the actual W time (e.g. 73±2% accuracy at 500 ms before W, arrow in Fig. 5B) and better than the best individual unit. Figure S5C–F shows the performance of the classifier for different individual subjects and different medial frontal lobe regions (Table S1).

We next constructed a pseudo-population by considering units across all experimental sessions and subjects (Hung et al., 2005; Mehring et al., 2003). We note that there is significant variability across subjects (e.g. Table S1 and Fig. S5D). At least partly, this variability can be accounted for by the different number of electrodes and recording locations across subjects. The pseudo-population approach considers all electrodes independently of the subject and assumes independence in the responses from different electrodes. The performance of the classifier increases with the number of units and as W is approached (Fig. 6A, S5E). As shown in Fig. 6A, a pseudo-population of 512 units pooled from across all frontal lobe regions yielded nearly 90% classification performance in identifying departure of neural activity from baseline 500 ms prior to W (and over 70% at 1000 ms before W; Fig. S5E). In other words, 500 ms before the subject reports the first time of becoming aware of the decision to perform a movement, a linear decoding algorithm based on a small neuronal ensemble can detect significant changes in the population activity on 90% of the trials (and in 70% of the trials 1000 ms before W).

Since we recorded from neurons in several different brain regions (Table 1), we considered neuronal pseudo-populations coming from distinct brain locations (Fig. 6B–C). Medial frontal lobe neurons clearly yielded higher classifier performance than medial temporal lobe neurons as expected based on the single neuron results (Fig. 6B). For instance, decoding performance of 70% is reached by 180 medial frontal units 840 ms prior to W, while 180 temporal lobe neurons achieve 70% performance only 80 ms before W (arrows in Fig. 6B). Within those neurons in the medial frontal lobe, neurons in SMA (including SMA-proper and pre-SMA) showed better decoding performance than the ACC units (Fig. 6C). For instance, decoding performance of 70% is achieved using the activity of 256 SMA units 980 ms prior to W but only 480 ms prior to W when using the activity of 256 ACC units. Alternatively, at 500 ms prior to W, decoding performance using the activity of 256 SMA neurons is over 80% but only 70% when using the activity of 256 ACC units (Fig. 6C). There was no significant difference in decoding performance when using activity from units in the left hemisphere (contra-lateral to the responding hand) versus units in the right

hemisphere (Fig. 6D). Additionally, the comparison of single units versus multi-units yielded similar decoding performance levels (Fig. 6E). Decoding performance for "D" cells started earlier than for "I" cells (Fig.s 6F). Note that this earlier response for "D" cells is not apparent in Fig. 4A emphasizing the importance of the population decoding approach as opposed to the averaging across units in Fig. 4A.

Thus far, we have demonstrated that as W time is approached, we can reliably detect significant departures from baseline firing rate at the population level. Next, we tested how precisely we can predict the *W time* based on the neuronal activity. We used the SVM classifier to predict the time point at which the subject reported making the decision to move (Experimental Procedures, Fig. 7). The algorithm detected the occurrence of W in 98% of the trials and only missed W in 2% of the trials. Figure 7D shows the distribution of predicted W times based on the activity of a pseudo-population of 512 units. This relatively simple linear algorithm predicted W to occur, on average, 152 ms prior to the actual reported W (median=100 ms prior to the reported W). There was a large spread around this mean, with a standard deviation of 370 ms. This spread seems to be consistent with our coarse estimations of the inaccuracies in the behavioral report of W times discussed above (Fig. S4D). Overall, our linear algorithm relying on a small ensemble of neurons is able to predict a W time that is within a few hundred ms of the actual W time reported by the subjects.

To examine whether the neuronal responses also represent information about the contents of volition, we recorded from 83 units (55 in medial frontal lobe and 28 in medial temporal lobe) in 3 additional subjects while they performed a variation of the task in which they not only chose the precise timing of the button press but also whether to press the button using their left or right hand (Haggard and Eimer, 1999). Some units showed a differential response depending on the hand choice (Fig. S7B–C) whereas other units showed changes that were independent of the hand choice (S7A). In most of the lateralized responses, the units showed a larger increase in firing rate when the subject chose the hand contra-lateral to the electrode's hemisphere. The neuronal population could extrapolate across hand choices to determine the volitional decision, as demonstrated by training the classifier to detect the onset of W using the neuronal responses from those trials in which subjects chose their right hand and testing the classifier's performance on those trials in which subjects chose their left hand (and vice versa) (Fig. S7D). Additionally, the neuronal population contained information about the contents of the volitional decision as evidenced by training the classifier to identify which hand the subject opted to use (Fig. S7E). We note that the weights for each unit are very different in Fig. S7D vs. S7E. Taken together, the results in this small sample suggest that essentially all the SMA units showed progressive changes in average firing rate for both hand choices, some units showed a stronger response to contra-lateral hand choices, and the population of units could indicate W regardless of hand choices and also predict the hand choice well above chance levels.

DISCUSSION

We present evidence that preconscious activity of small assemblies of single neurons in the medial frontal lobe not only precedes volition but can also predict volition and its time of occurrence on a single trial basis. The experimental paradigm used here to capture the volition timing has been, since its inception, a topic of lively debate (e.g., (Libet, 1985) and comments therein). Variables such as attention, motor preparation, decision-making and intention have been invoked to explain early changes prior to W. The reporting of W is far from trivial, as subjects need to decide when they first felt the urge to move and then report it only later. However, our analyses show that inaccuracies of up to ~200 ms in the report of W do not significantly change the number of neurons altering their activity before W (Fig. S4D). We also showed that alternative definitions of the "baseline period" to the ones used

in the text also yield similar conclusions (Fig. S3E), that subjects were not performing "cued" movements (Fig. 1D, S3A) and that there were no significant differences between short and long trials (Fig. S3B). While these methodological considerations are pertinent, the early observations reporting scalp-recorded electroencephalographic readiness potential (*Bereitschaftpotential*) preceding volition (Colebatch, 2007; Deecke et al., 1969; Gilden et al., 1966; Libet et al., 1983; Shibasaki and Hallett, 2006) have been since replicated by several investigators and withstood the challenge of time (Haggard, 2005, 2008).

In human studies, it is difficult to make accurate timing estimates based on BOLD changes and it is difficult to make accurate location estimates based on scalp signals. The study of volitional control in non-human primates presents a formidable challenge. Our study combines high spatial and temporal resolution and provides bounds for the spatial and temporal onset of volitional control. Our findings suggest a preconscious event observed at the single neuron level in the SMA prior to subjects' perceived urge to move. These findings bring to mind Eccle's sweeping hypothesis that "in all voluntary movements the initial neuronal event is in the supplementary motor areas (SMA) of both cerebral hemispheres" (Eccles, 1982). However, since our recordings were limited to regions of clinical interest, it is not clear that indeed the *earliest* neuronal event occurs at the SMA and not a different region we did no record from.

Some units show a progressive increase in average firing rate as W is approached whereas other units show a decrease in firing rate. These response patterns do not reveal anything about whether these units are excitatory or inhibitory. Within our sample, we find that the units recruited prior to volition are in regions of the medial wall of the frontal lobe, known to be involved in the planning, initiation, and execution of motor acts (Picard and Strick, 1996). The ramp up in activity that we describe here is reminiscent of similar slow changes in activity that have been observed in delay tasks in macaque monkeys in frontal and parietal cortex areas (e.g. (Andersen and Buneo, 2002; Boussaoud and Wise, 1993; Freedman et al., 2001; Fuster, 2001; Gold and Shadlen, 2007; Maimon and Assad, 2006a, [b]; Miller, 2000; Rainer et al., 1999; Romo et al., 1999; Romo and Schultz, 1992; Russo et al., 2002; Shima and Tanji, 2000; Tanji, 1994)). Changes preceding W were significantly less frequent and robust in the temporal lobe where the neurons studied contributed little to the prediction of W (Fig. 4D, 6B, S1 and Table 1). The changes in firing rate of medial temporal lobe neurons, particularly in the vicinity of W, may indicate their role in holding or recalling the handle's position in memory. Within the medial frontal lobe, higher performance in decoding volition is achieved earlier when decoding is based on SMA compared to ACC neurons. Numerous studies have implicated the SMA in the early representation of preparation for movement (Amador and Fried, 2004; Brinkman, 1984; Erdler et al., 2000; Fried et al., 1991; Ikeda et al., 2002; Laplane et al., 1977; Lau et al., 2004a; Lau et al., 2004b; Lim et al., 1994; Scepkowski and Cronin-Golomb, 2003; Shima and Tanji, 2000; Tanji, 1994; Thaler et al., 1995). A recent fMRI study (Lau et al., 2004a) showed activation of the SMA (albeit in pre-SMA rather than SMA-proper) when subjects attended to the timing of the intention to move, compared to the actual movement itself. In the current study, ACC neurons are also recruited several hundred ms prior to volition. Recent fMRI data showed that intentions covertly held by human subjects prior to overt response were best decoded by activity in mesial prefrontal cortex, an area which includes the rostral ACC (Haynes et al., 2007). In monkeys, single neuron activity prior to movement occurs in the ACC, though later than in the SMA (Russo et al., 2002).

Our sample of recording locations is far from exhaustive. Other brain areas from which we did not record in the current study could also contribute to volition. Parietal areas show strong responses to *cued* movements, interpreted to represent the animal's motor intentions (Andersen and Buneo, 2002; Boussaoud and Wise, 1993; Cui and Andersen, 2007; Shenoy

et al., 2003). Lateral intraparietal neurons exhibit firing rate elevation reaching a consistent value at the time of proactive, rather than reactive, arm movements (Maimon and Assad, 2006a). There is also significant evidence that links activity in the human parietal lobe to conscious intentions (Assal et al., 2007; Desmurget et al., 2009; Desmurget and Sirigu, 2009; Farrer et al., 2008; Sirigu et al., 2004; Sirigu et al., 1999). A recent study has shown striking evidence that electrical stimulation in parietal cortex elicited an urge to move and showed a dissociation between the effect of stimulation in parietal and premotor areas (Desmurget et al., 2009). In a rare opportunity, we recorded from 13 units in the right posterior parietal cortex in one subject. We observed 3 units (e.g. Fig. S8) that showed pre-W increases in average firing rate (similar to Fig. 3). The nature of the interaction between parietal and premotor cortex is an important question for future studies (Desmurget and Sirigu, 2009; Haggard, 2008).

In addition to a yes/no decision and its timing, a key aspect of volition is the possibility of deciding among multiple alternatives. This distinction has been formalized in the framework of characterizing the “what”, “when” and “whether” of intentional action (Brass and Haggard, 2008). These different cognitive processes may be instantiated by separate neural circuits (Brass and Haggard, 2008; Lau et al., 2004a; Soon et al., 2008; Trevena and Miller, 2002). Here we observed that several SMA neurons showed differential responses between hand choices (Fig. S7B–C). In our small sample, those neurons showed stronger activation when subjects opted to use the contra-lateral hand, perhaps suggesting a role in motor preparation. Yet, we note that the neuronal responses started hundreds of ms (and sometimes even several seconds; Fig. 3) before W. Also, while the subjects always used their right hand in the main variant of the task, we still did not see a difference in decoder performance when using the neural data from the right or left hemispheres (Fig. 6D). These neurons still showed a progressive change in the response in those trials when subjects used the ipsi-lateral hand. Moreover, the classifier could extrapolate across hands (Fig. S7). We can predict the volitional content (right versus left hand choice) from the population activity in SMA (Fig. S7). Scalp recordings have shown that the readiness potential was not affected by hand choice but lateralized readiness potentials did show differences contingent on the hand choice (Haggard and Eimer, 1999) (and fMRI in (Khonsari et al., 2007)(Soon et al., 2008)). Electrical stimulation studies point to contra-lateral biases in pre-volitional responses (Fried et al 1991, Desmurget and Sirigu 2009). Laterality is a complex issue and the results reported in previous scalp EEG, fMRI and electrical stimulation studies likely involve averaging over large numbers of neurons. The “overall” average activity may reveal more consistent contra-lateral biases than the neuronal responses described here.

Several hundreds of ms prior to volition, a neural process, explicit at the single neuron level, is set in motion. At the population level and also in several example units, activity peaks before W (Fig. 3C,G,H,I,J,K,M and 4A). As W time is approached, an increasing number of neurons are recruited (Fig. 4D). Several studies have attempted to make a link between the neural events that precede W and the feeling of “will” (Brass and Haggard, 2008; Fourneret et al., 2002; Haggard, 2008; Libet, 1985; Soon et al., 2008; Trevena and Miller, 2002; Yazawa et al., 2000). The relationship between neural activity in cortex preceding motor output and the emergence of consciousness remains a topic of debate (Fourneret et al., 2002; Haggard, 2008). Although it remains unclear whether the emergence of volition is causally related to the neuronal changes described, the information conveyed by a small population of such neurons in the medial frontal lobe is sufficient to predict the onset of volition several hundreds of ms before subjects’ awareness. This neuronal process suggests a mechanism whereby the feeling of will arises once integration of firing of recruited medial frontal neurons crosses a threshold (Gold and Shadlen, 2007; Libet et al., 1983; Matsuhashi and Hallett, 2008). Indeed an integrate-and-fire model that uses the medial frontal units as input could well implement this mechanism, reaching threshold within a few hundred ms of W

(Fig. S5G–I). While this is not a conclusive mechanistic proof or description of the neuronal circuitry involved in this task, this simple model suggests a potential biophysically-plausible circuit for eliciting volitionally-guided behavior that is consistent with our empirical observations and the ones from previous studies. Taken together, these findings lend support to the view that the experience of will emerges as *the culmination of* premotor activity (probably in combination with networks in parietal cortex) starting several hundreds of ms before awareness. The scientific, philosophical, and societal implications of these findings remain open for debate.

EXPERIMENTAL PROCEDURES

Subjects and recordings

The data in the current study come from 28 recording sessions in twelve patients with pharmacologically intractable epilepsy (eight right handed; seven males; 15–46 years old). The patients were implanted with chronic depth electrodes for 7–10 days to determine the seizure focus for possible surgical resection. It should be kept in mind that these recordings come from patients with a neurological disorder; however, we note that most of the data are from regions that were found to be non-epileptogenic.

We report data from the following sites in the medial frontal lobe: supplementary motor area (SMA) corresponding to Brodmann's area 6, including *SMA proper* and the *pre-supplementary motor area* (pre-SMA) (Picard and Strick, 1996), anterior cingulate cortex (ACC) corresponding to Brodmann's area 24, including the dorsal ACC and the rostral ACC (McCormick et al., 2006). There are no definitive criteria to distinguish SMA and pre-SMA based on imaging; the border between SMA- proper and pre-SMA was determined at the level of the anterior commisure (VAC line) (Picard and Strick, 1996, 2001; Vorobiev et al., 1998). In addition, we recorded from neurons in the temporal lobe (Table 1). All studies conformed to the guidelines of the Medical Institutional Review Board at UCLA and all patients provided their consent to participate in the study. The electrode locations were based exclusively on clinical criteria and were verified by co-registering the post-implant CT image to the pre-operative structural MRI using Vitrea (Vital Images Inc.). Due to the differences in the number and location of electrodes, there is a considerable variability across subjects (e.g. Table S1 and Fig. S5D). Each electrode probe had 9 micro-wires at its end, eight recording channels and one reference (Fried et al., 1999). The differential signal from the micro-wires was amplified using a 64-channel Neuralynx system (Tucson, Arizona), filtered between 1–9000 Hz and sampled at 28 kHz. After spike sorting, the units were classified as "single units" or "multi-units" based on the automatic labeling criteria described in (Tankus et al., 2009) (e.g. Fig. 2A–B).

Experiment design

Subjects sat in bed facing a laptop computer depicting an analogue clock. The clock handle rotated with a period of 2,568 ms around the clock's circumference (clock tick=42.8 ms). Subjects were instructed to place their right index finger on a key on the laptop keyboard, to wait for at least one complete clock revolution of the handle, and then press the key whenever they "felt the urge" to do so (Fig. 1). Pressing the key (P) stopped the movement of the handle, and subjects were then asked to move the clock handle back to the spot where it had been when they first felt the urge to move. This point in time was referred to as the onset time of conscious free will (W). Trials were repeated in blocks of 25. Because of delays between index finger motion onset and the keyboard press, our measurement of P is delayed with respect to the actual motor onset (Fig. S3C–D). The actual motion onset would be even closer to W than what we report in Fig. 1D. Experimental trials that fulfilled any one of the following criteria were excluded from the analyses: (1) W and P times were the

same (5% of the trials); (2) W time preceded P time by >1500ms (<1% of the trials); (3) Trial duration lasted >20 seconds (3% of the trials); (4) Trials when the subject did not wait for one full rotation of the clock (10% of the trials); (5) One session from one subject was not considered further because there was only 1 good trial. These criteria are similar to those used in the original experiments by Libet and subsequent studies (Libet et al., 1983). The average number of trials per patient was 70 (range 25 – 128).

Three subjects performed a modified version of the task where they were allowed to choose not only the time of action but also which hand to use. These subjects could tap the keyboard with either their left or right index finger (Fig. S7).

Spiking activity

The raw data were band-pass filtered between 300 and 3000Hz and thresholded for detection of potential spikes. Action potentials were clustered using a clustering algorithm and manually sorted as spikes or electrical noise (Quian Quiroga et al., 2005). The classification between single unit and multi-unit was performed automatically based on the criteria described in (Tankus et al., 2009).

Data analysis

Classification of individual units—Firing rate was defined as the spike count in the (−2500, −1500) ms window (baseline) and in the −400 ms to 0 ms relative to W (pre-W) (Fig. S3E). We compared firing rates using a non-parametric ranksum test and a threshold criterion of $p < 0.01$ (similar results were observed using a paired two-tailed t-test). An analysis using a sliding window is presented in Fig. 4. In Fig. S1 we compared the changes in firing rate against those expected under three different null hypotheses (Supplementary Text). We classified the response of all 128 units responding significantly before W (Table 1) as either showing increase in firing rate with respect to baseline (“I”, n=55) or decrease in firing rate with respect to baseline (“D”, n=73). To plot Fig. 4A–C and S1G, the responses were normalized by subtracting the baseline activity and dividing by the maximum firing rate for “I” cells (or dividing by the absolute value of the minimum firing rate for “D” cells). After normalization, the responses were averaged.

Statistical classifier—Figures 5–7 in the main text as well as Fig. S4 use a Support Vector Machine (SVM) (Hung et al., 2005) classifier to quantify whether the neuronal ensemble showed changes in their firing patterns before W. The classifier yields a measure of performance at the single-trial level, as opposed to the typical *Bereitschaftspotential* averaged over a large number of repetitions (Colebatch, 2007; Erdler et al., 2000; Haggard and Eimer, 1999; Libet et al., 1983; Ohara et al., 2006; Yazawa et al., 2000). In Fig. 5B, 5 and S4, we asked whether the classifier could discriminate the neuronal responses from baseline activity at a time t prior to W (the Supplementary Text provides details about the classifier analyses). We used a cross-validation procedure whereby we randomly chose 70% of the trials for training and the remaining 30% of the trials were used to evaluate the classifier performance. Importantly, the performance of the classifier was evaluated with *independent data* that was not seen by the classifier during training (i.e., there was no overlap between the training and test data). The performance of the classifier at time t indicates the percentage of test trials correctly discriminated from baseline at a time t prior to W. Error bars in the classifier performance plots denote one standard error and are based on this cross-validation procedure. We also considered different subpopulations to train the classifier: right versus left hemisphere (Fig. 6D), single units versus multi-units (Fig. 6E) and different recording locations (Fig. 6B–C).

Prediction of W time—Figure 7 in the main text describes the performance of the classifier in predicting the time of volition onset (W). The procedure is described in the Supplementary Text.

Accuracy of W—Reporting W accurately is not trivial. Therefore, it is expected that there could be a variation between the reported W and the internal onset of the decision/urge to move. It is not easy to estimate this variability (Joordens et al., 2002). To quantify the impact of changes in W time on the spiking responses and our analyses, we simulated inaccuracies in W by adding a fixed temporal bias (Fig. S4D1) or random jitter (Fig. S4D2) to W.

Integrate-and-fire model—We speculate in the main text that the urge/decision may arise when a threshold is crossed after a cumulative increase in activity in the medial frontal lobe neuronal ensemble (Crick and Koch, 2003). The Supplementary Text describes an integrate-and-fire model that quantifies and implements this idea (Fig. S5G–I).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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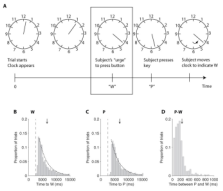

Fig. 1.

A. Schematic diagram depicting the experimental paradigm (Libet et al., 1983). Subjects were shown an analog clock and were asked to press a key with their right index finger, at will, anytime after one rotation of the clock. After the key press event (“P”), the clock dial stopped and subjects were asked to indicate the time of onset of the “urge/decision” to press the key (“W”). **B–D**: Distribution of W times, P times and P-W across trials and subjects. Bin size=100 ms (**B, C**) and 42.8 ms (**D**). The arrow shows the mean of the distribution (6071±3005 ms; 6264±3019 ms and 193±261 ms, mean±SD in **B**, **C** and **D** respectively). Medians=4964 ms, 5156 ms, 171 ms respectively. Ranges=[2795,19769] ms, [2795, 19812] ms, [43, 1455] ms respectively. W and P times are measured with respect to the trial onset time at t=0. The vertical dashed line in **B** and **C** indicates the first revolution of the clock. These distributions and mean values are very similar to those reported in earlier implementations of the same paradigm (e.g. (Haggard, 2008; Haggard and Eimer, 1999; Libet et al., 1983)). The dotted line in **B** and **C** shows an exponential fit to the behavioral data. The coarse exponential fit suggests that the response hazard function is approximately uniformly distributed (Rausand and Hoyland, 2004).

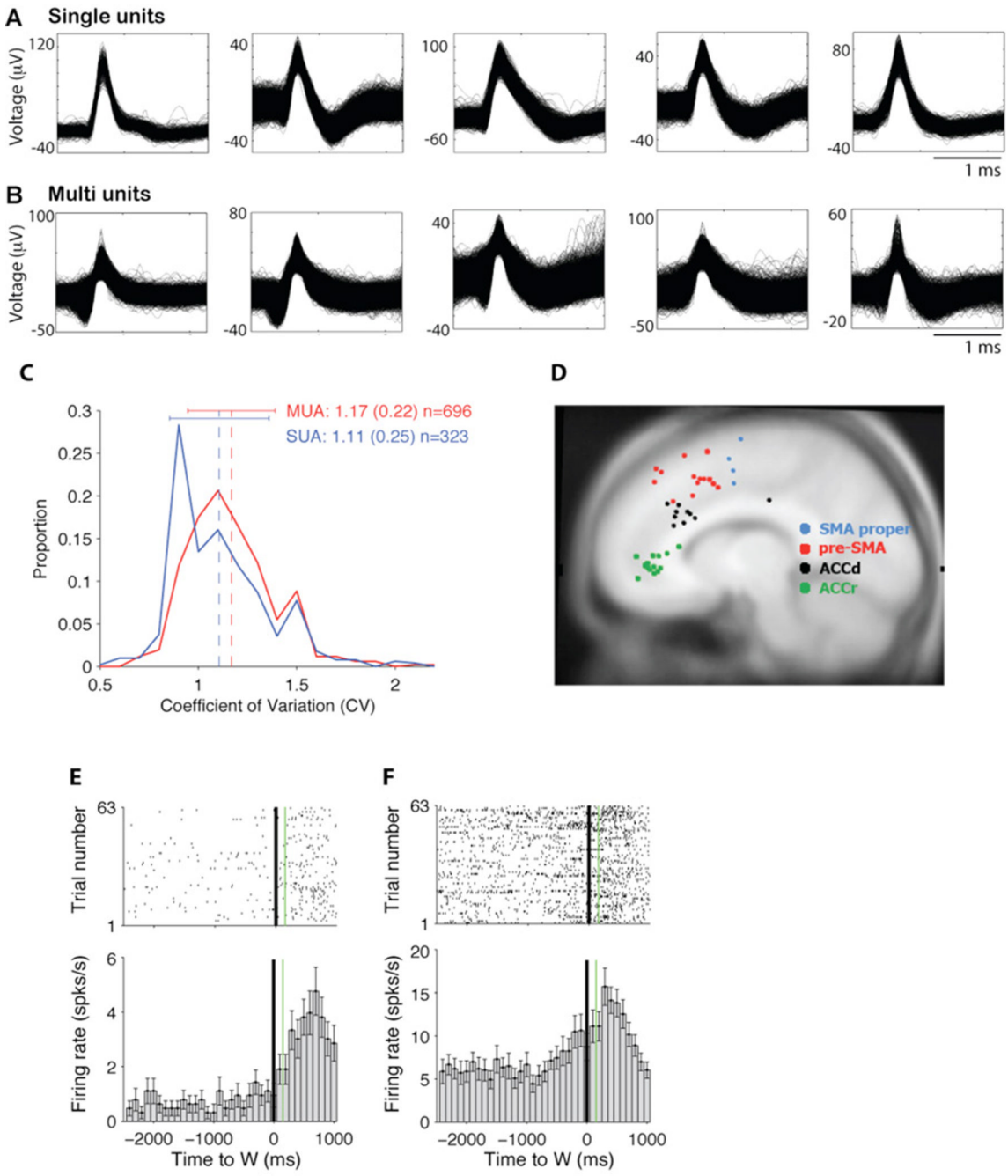

Fig. 2.

A–B. Example waveforms for five single units (**A**) and five multi-units (**B**). After spike sorting, units were classified into single units or multi-units according to the criteria described in (Tankus et al., 2009). **C**. Distribution of the coefficient of variation of the interspike interval distribution for MUA (red) and SUA (blue). The dashed lines indicate the mean of the distribution and the horizontal bars denote one standard deviation. **D**. Anatomical location of electrodes in the frontal lobe displayed on a Montreal Neurological Institute (MNI) brain (average of 305 brains) (Collins et al., 1994). Each electrode included 8 recording microwires. (**E–F**) Raster plots and histograms showing the responses of a neuron in left ACCd displaying a significant response after W (ranksum test, $p<10^{-6}$) (**E**),

and one neuron in left pre-SMA with response onset prior to W (ranksum test, $p<10^{-3}$) (**F**). All plots are aligned to W (time=0). Error bars indicate SEM (n=63 repetitions). The green line in the PSTH denotes the average time of key press across all trials. Bin size for the PSTH=100 ms.

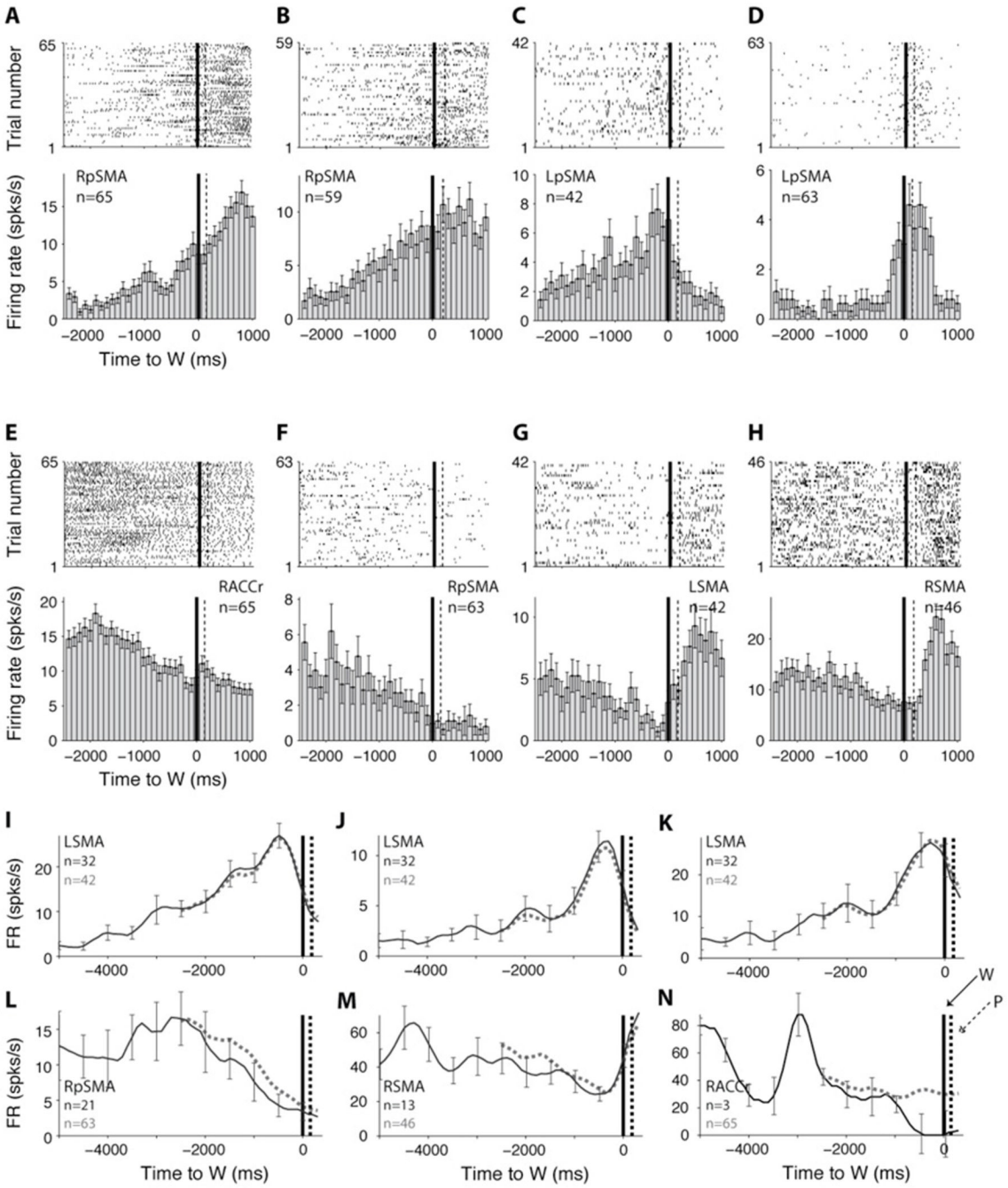

Fig. 3.

A–H. Examples of response profiles. (**A–D**) Neurons increasing their firing rates prior to W ($p < 10^{-5}$, 10^{-5}, 10^{-7}, and 10^{-5} respectively). (**E–F**) Neurons decreasing their firing rates prior to W ($p < 10^{-5}$, 10^{-4} respectively). (**G–H**) Neurons decreasing their firing rate prior to W and then increasing their firing rates around W ($p < 10^{-3}$, 10^{-5} respectively). The conventions are as in Fig. 2E–F.

(**I–N**). Examples of responses from several units that started to change their firing rate before the baseline period used in the text (−2500 to −1500 ms with respect to W). The responses are aligned to W (vertical black line); the vertical dashed line denotes the mean P. Only those trials where W occurred more than 5000 ms after the first turn of the clock are

shown in the black trace. The dotted red trace shows all trials starting from 2500 ms before W (the black curve and the red curve do not overlap perfectly because there are more trials averaged in the red curve; the number of trials is indicated on the left of each subplot). The location of each unit is indicated in each subplot. Error bars denote SEM and are shown only every 500 ms.

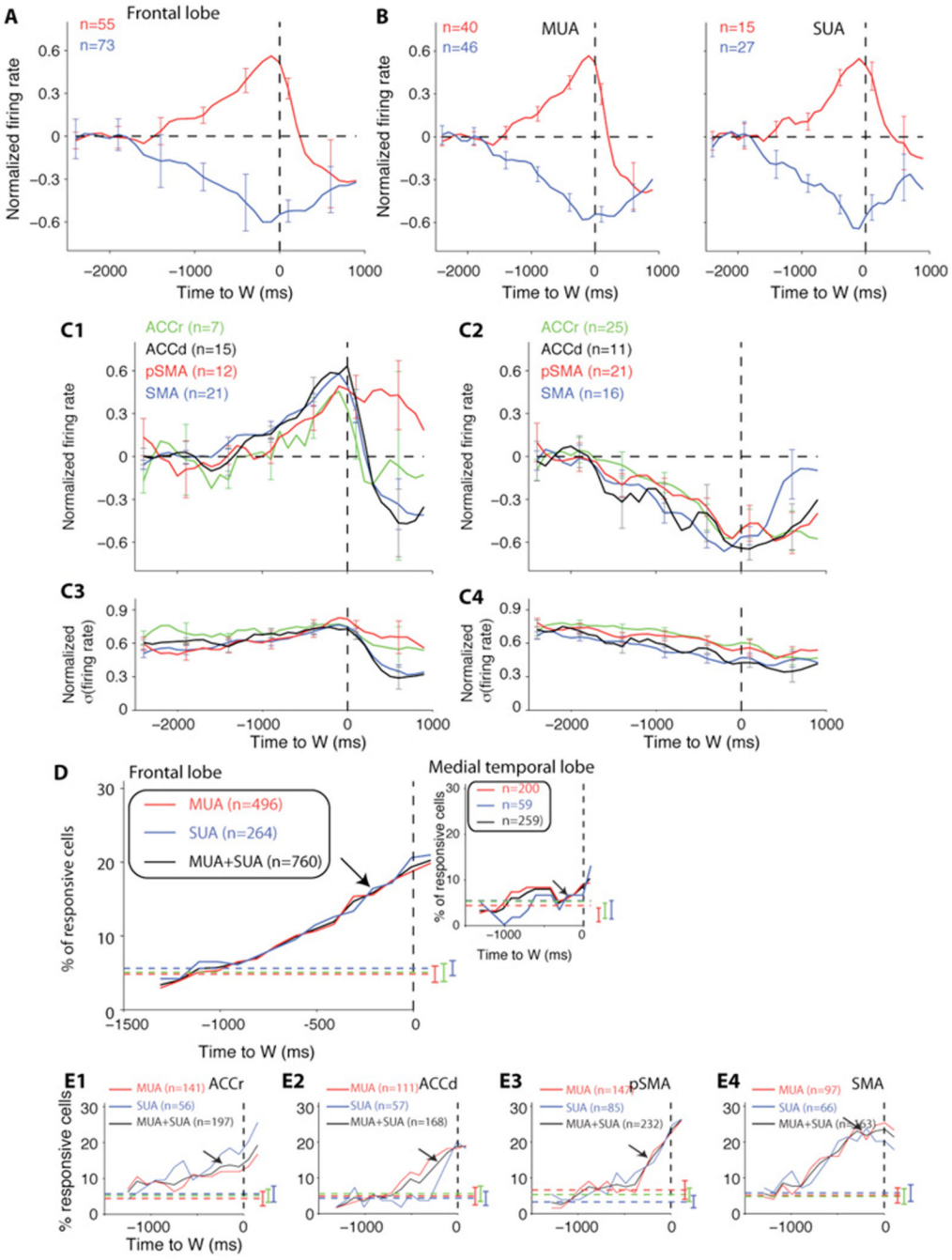

Fig. 4.

A. Average normalized response profile of all neurons in the frontal lobe responding prior to W, separated by whether they increase (red) or decrease (blue) their rate as W is approached (referred to as “I” and “D” respectively in the text for Increases or Decreases in firing rate). For each neuron, the baseline activity (−2500ms to −1500ms relative to W) was subtracted. For units showing increased activity before W (red), the PSTH (bin=100ms) was normalized by the maximum firing rate and for units showing decreased neural activity before W (blue), the PSTH was normalized by the minimum firing rate. Note that the responses start well before the interval used to define units as “I” or “D” (in contrast to Fig. S1G). Error bars denote SEM and are shown only every 500 ms for clarity.

B. Average normalized response profile showing the temporal evolution of the responses for "I" (red) and "D" (blue) cells for MUA (**left**) and SUA (**right**).
C1–C2. Average normalized firing rate of all "I" cells (**C1**) and "D" cells (**C2**) responding prior to W in each medial frontal lobe region. This plot includes both MUA and SUA (cf. **B**). Error bars denote SEM and are show only every 500 ms for clarity.
C3/C4. Average normalized standard deviation of the firing rate of all "I" cells (**C3**) and "D" cells (**C4**) responding prior to W in each medial frontal lobe region. The format and conventions are the same as in **C1–C2**. For each unit, we computed the standard deviation of the firing rate across trials in each time bin and we normalized by the maximum standard deviation across all time bins.
D. Percentage of frontal lobe neurons with significant change in firing rate compared with baseline (ranksum, $p<0.01$) as a function of time before W (Experimental Procedures). For each unit, we calculated the baseline firing rate in the window −2500ms to −1500ms relative to W (see Fig. S3E for earlier definitions of baseline period). Next, we calculated the firing rate in a 400 ms sliding window (100 ms steps) starting at time - 1500 ms to 0 ms and assessed significant changes from baseline using a ranksum test. The red and blue traces show the corresponding analyses restricted to MUA (red) and SUA (blue). The arrow indicates the percentage reported in Table 1. The horizontal dashed lines show the expected percentage (±SD) according to three different null models as described in Fig. S1 (red="Random W", green="Poisson", blue="ISI conserved"; Fig. S1).
E. Percent of neurons across brain regions with significant change in firing rate (compared with baseline) as a function of time before W.

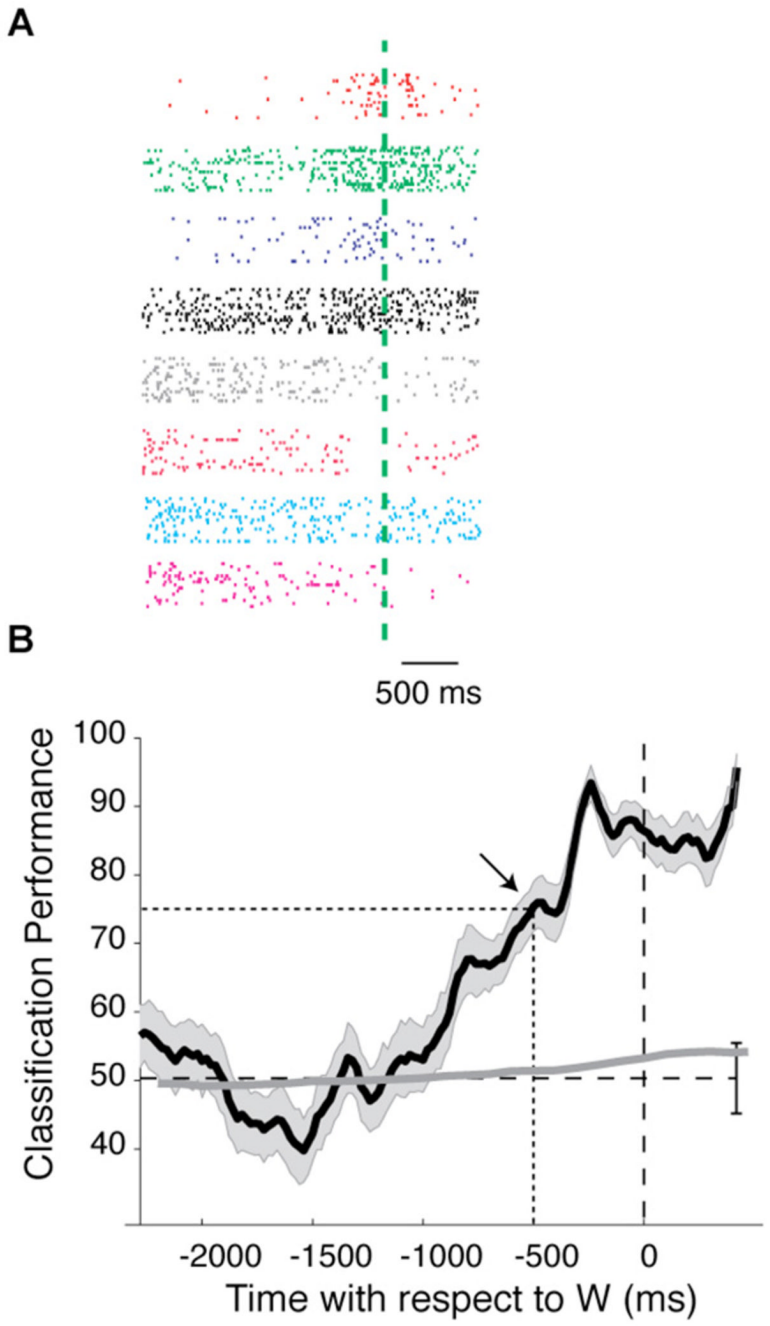

Fig. 5.

Discriminating activity from baseline on a trial-by-trial basis using a statistical classifier. **A**. Responses of 8 units (each in a different color) during one experimental session. Only 15 trials, randomly selected from the 53 trials in this session, are shown here for each unit. The vertical dashed line indicates the W time. **B**. Performance of a support vector machine (SVM) classifier in distinguishing changes in population activity with respect to baseline. At each time point *t* with respect to W (vertical dashed line), we considered the response of each neuron during the interval [t−200 ms;t+200 ms). We used a statistical classifier to assign the response of each neuron or each neuronal population as belonging to time *t* or the baseline period [−2500 ms; −2100 ms). The y-axis shows the performance of the classifier;

the horizontal dashed line corresponds to chance performance obtained by random permutation of the training labels. We show the average performance level across all individual neurons in this session (gray). We next considered the entire ensemble of 37 units recorded during this experimental session (including single unit and multi-units, 22 in SMA, 8 in ACC, 7 in the medial temporal lobe). The black curve shows the performance of the classifier based on the ensemble activity; the gray shaded region indicates SEM based on 100 cross-validation steps (different random split of the data into a training set and a test set). In all cases, the reported performance levels are computed using test data *not seen* by the classifier during training. The two units illustrated in Fig. 2 were recorded during this session and are therefore included in the analysis.

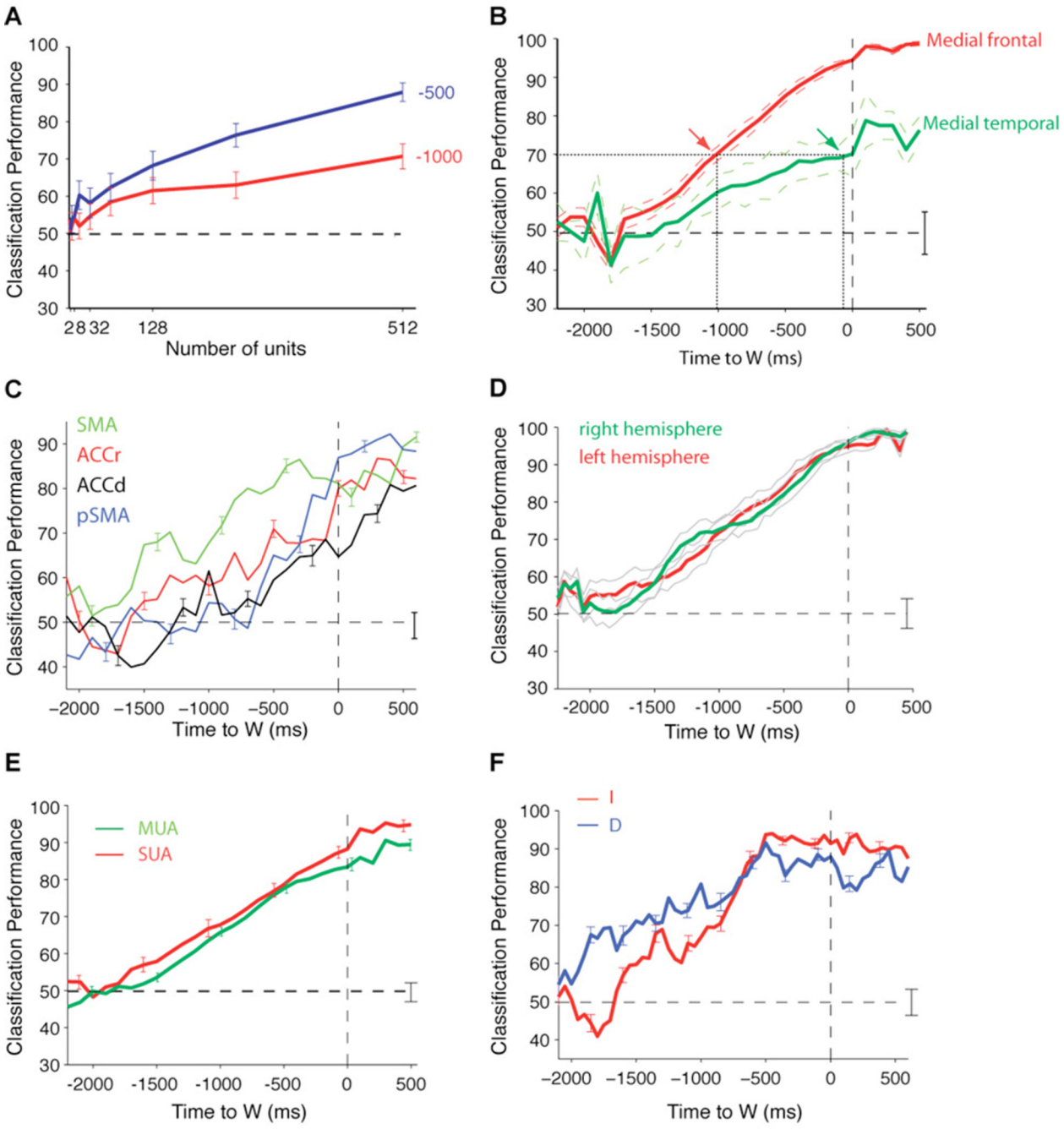

Fig. 6.

Single-trial decoding of response changes from neuronal population activity. **A**. Performance of the decoding classifier using a pseudo-population of varying number of units randomly sampled from the entire data set of 1019 units including both frontal and temporal regions. The horizontal dashed line indicates chance performance (50%). The red line corresponds to the classifier performance 1000 ms before W and the blue line corresponds to the classifier performance 500 ms before W as a function of the number of units used. The error bars indicate one standard deviation obtained by cross-validation from 100 random choices of the units and repetitions used for training the classifier. In all cases, the reported performance corresponds to test data not seen by the classifier during training.

B. Comparison of decoding performance based on medial frontal (red) versus medial temporal (green) units (*n*=180 units). Note the significant advantage of medial frontal neurons over medial temporal ones. The analysis is the same as in part **A** except that here we select specific regions that are used to train and test the decoder. **C**. Comparison of the decoding performance based on 150 SMA (green), 150 pre-SMA (blue), 150 rostral ACC (red) and 150 dorsal ACC units (black). The analysis and format are the same as in part **A**. Note the higher classification performance of SMA over the other locations. **D**. Comparison of classification performance using units from the right hemisphere (green) versus units from the left hemisphere (red). The format and conventions follow the ones in part **A**. A population of *n*=268 units in each hemisphere was used (all locations combined). The horizontal dashed line shows chance performance level and the error bars were estimated by randomly shuffling the preW/baseline labels. The gray lines around the main curves show SEM over 100 cross-validation iterations. **E.** Comparison of classification performance using single units (red) vs. multi-units (green). A spike-sorting algorithm was used to discriminate single units (SUA) from the recorded multi-unit activity (MUA) and we automatically assigned clusters to SUA or MUA (Experimental Procedures). Here we compare the decoding performance using single-units (red, *n*=256) versus multi-units (green, *n*=256) (all locations and hemispheres combined). The format and conventions follow the ones in **A**. The horizontal dashed line shows chance performance level and the error bars were estimated by randomly shuffling the preW/baseline labels (one standard error over 100 cross-validation iterations). **F.** Comparison of classification performance using “I” cells (red, 50 units) vs. “D” cells (blue, 50 units). In this figure, all locations are combined and SUA and MUA are combined. The format and conventions are the same as in part **A**.

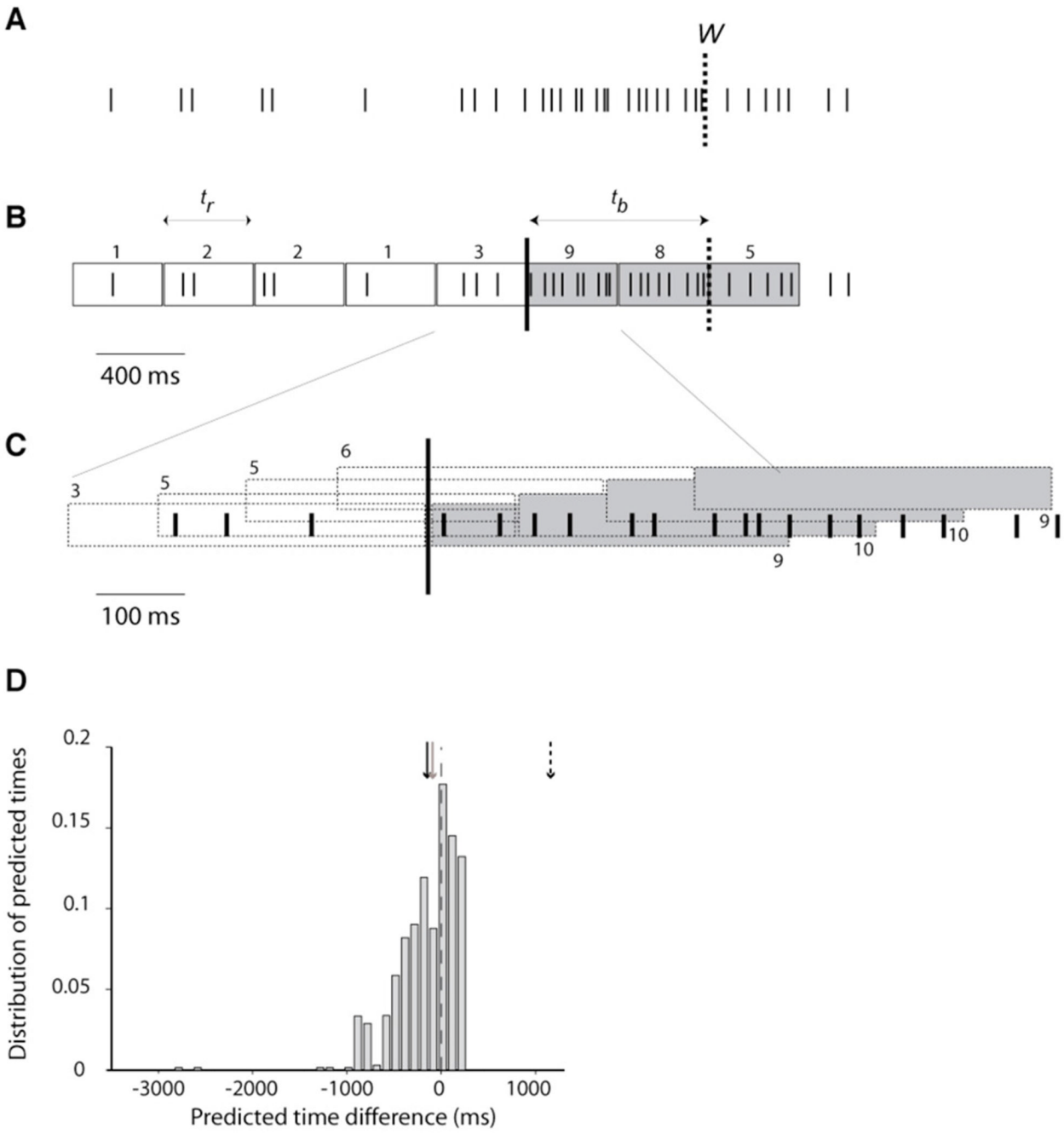

Fig. 7.

Predicting the time of "urge/decision" onset (W). **A–C**. An SVM algorithm was used to predict the time of "urge/decision" onset (W) based on the population spiking data using 512 units. The activity of each unit was aligned to W to be able to compare activity across different recording sessions and subjects. The classifier was trained to recognize whether W had been reached or not, using windows of size 400 ms (Experimental Procedures). The binary classifier was trained using 70% of the trials and its performance was tested on the remaining 30% of the trials. The analysis window was shifted from −3500 ms up to +1000 ms with respect to W. During testing, the predicted W time was defined as the first time point when 3 out of 4 consecutive windows yielded a label indicating the occurrence of W.

A. Single trial spike train example marking the position of the spikes and W. **B**. Spike counts in windows of size t_r=400 ms. Gray rectangles denote windows where W occurred within a time t_b ms. **C**. Spike count windows overlapped by 100 ms. **D**. Distribution of the difference between the predicted time and W (the real W corresponds to t=0 and is denoted here by the vertical dashed line). Bin size=100 ms, n=3963 trials (using cross-validation). The black and gray arrows denote the mean (−152 ms) and median (−100 ms) of the distribution respectively (standard deviation=370 ms). The dashed arrow indicates the mean value for a control case where training labels were assigned randomly (mean=1153 ms, standard deviation=995 ms). The fraction of missed trials (where the classifier could not detect W) was 2% (91% for the random label control case).

Table 1

Anatomical distribution of responses (12 subjects). Total number of cells recorded, number [and percentages] of cells in each region responding prior to and after W (based on a ranksum test, $p<0.01$, see Experimental Procedures). The numbers in parenthesis indicate the number of multi-units and single-units. SMA –supplementary motor area; ACCd – dorsal aspect of anterior cingulate cortex (including 20 postcentral units); ACCr – rostral aspect of ACC (including 26 medial cingulate units); A – amygdala; H – hippocampus; PHG – parahippocampal gyrus; EC –entorhinal cortex; ST –superior temporal gyrus (including 4 units in the temporal pole) (see also Table S1 and Table S2).

Frontal Lobe	**ACCr**	**ACCd**	**pre-SMA**	**SMA proper**	**Total**
# of recorded cells	197 (141+56)	168 (111+57)	232 (147+85)	163 (97+66)	760 (496+264)
Before W	32 [16%] (23+9)	26 [15%] (18+8)	33 [14%] (18+15)	37 [23%] (20+17)	128 [17%] (79+49)
After W	24 [12%] (15+9)	22 [13%] (14+8)	35 [15%] (22+13)	17 [10%] (9+8)	98 [13%] (60+38)

Temporal Lobe	**A**	**H**	**EC**	**ST**	**PHG**	**Total**
# of recorded cells	24 (19+5)	51 (34+17)	127 (94+33)	33 (31+2)	24 (22+2)	259 (200+59)
Before W	2 [8%] (2+0)	4 [8%] (3+1)	9 [7%] (6+3)	3 [9%] (3+0)	2 [8%] (2+0)	20 [8%] (16+4)
After W	0 [0%] (0+0)	7 [14%] (4+3)	7 [6%] (5+2)	8 [24%] (8+0)	6 [25%] (1+5)	28 [11%] (18+10)