LETTER

Accumulation of Neural Activity in the Posterior Insula Encodes the Passage of Time

Marc Wittmann$^{1,3}$, Alan N. Simmons$^{1,3}$, Jennifer L. Aron$^2$, Martin P. Paulus$^{1,3}$

$^1$Department of Psychiatry, University of California San Diego, La Jolla, CA 92093, USA. $^2$Department of Neurosciences, University of California San Diego, La Jolla, CA 92093, USA. $^3$Veterans Affairs San Diego Healthcare System, San Diego, CA 92161, USA.
The experience of time, i.e. the estimation of duration, is fundamental for perception and behavior and, therefore, essential for the survival of the individual organism\(^1\text{-}^3\). Over the last decades, neuroimaging, neurophysiological and clinical neuropsychological studies have pointed to many different brain areas involved in the processing of time\(^4\text{-}^8\). However, the core neural substrates and the processes accounting for the encoding of duration, which could form a timekeeping mechanism (essentially, a ‘neural clock’), are still unknown. Here we present evidence of neurophysiological activity in circumscribed areas of the human brain that is involved in the encoding of duration. Time-activity curves of neural activation derived from event-related functional magnetic resonance imaging (fMRI) during a time estimation task show that bilateral posterior insula as well as superior temporal and inferior parietal cortices build up activation when individuals are presented with 9 or 18 seconds tone intervals. Since the build up of neuronal activation peaks at the end of the interval, it appears that this accumulator-type activity encodes duration. Because of the close connection between posterior insula and ascending internal body signals\(^9\text{-}^{10}\), the accumulation of physiological changes in body states might constitute our experience of time. These results could be the starting point for a neural model of human time perception in the multiple-seconds range in which specific brain regions accumulate brain activity for the representation of duration.

To date, there is still no conclusive answer to the question of which areas of the brain and what kind of neurophysiological processes account for the experience of duration in humans. A number of different brain areas have been implicated in a
postulated time keeping mechanism: notably, the cerebellum\textsuperscript{5}, the right posterior parietal cortex\textsuperscript{4}, the right prefrontal cortex\textsuperscript{8}, and fronto- (SMA) striatal circuits\textsuperscript{7,11-13}. The involvement of multiple brain areas in the perception of time may be due to different temporal-processing components that are not necessarily related to the encoding of duration, e.g. attention, working memory and decision-making\textsuperscript{6,14}. Neural processes across different brain areas also depend on the duration of the judged intervals: specifically, millisecond timing is governed by different processes than time perception in the seconds or multiple-seconds range\textsuperscript{3, 8, 15, 16}.

However, there is also no consensus as to what mechanisms account for our sense of time. The most prominent models over the last years have been variants of a pacemaker-accumulator clock where an oscillator produces a series of pulses and the number of pulses recorded over a given time span represents experienced duration\textsuperscript{17-19}. Other theoretical models assume specific neuronal system properties for encoding time not related to a pacemaker\textsuperscript{20-22}, or propose that memory decay processes are involved in time perception\textsuperscript{23}.

Functional magnetic resonance imaging (fMRI) studies have revealed that several brain areas engage during various time perception tasks which employ time intervals up to a few seconds\textsuperscript{8}. Due to the temporal constraints of the method (with data acquisition times typically near 2 seconds) the detection of neurophysiological changes over time is not possible for these short time intervals. Here we present the missing link for a neural theory of time perception for multiple-second intervals: we show empirical evidence of neurophysiological activity in specific areas of the brain (recorded with fMRI) related to the encoding of durations up to 18 s. Fourteen human subjects were instructed to reproduce tone intervals with 3, 9, and 18 s duration
during fMRI (Fig. 1). Each trial consisted of two consecutive phases: the encoding and the reproduction phases, respectively. In the encoding phase, participants listened to a 1.2 kHz tone. After a short pause, the reproduction phase was started and consisted of the presentation of a 2 kHz tone. In this phase, participants had to stop the presentation of this second tone when they estimated that it had reached the length of the first tone. In the control task, subjects had to listen to a 2 kHz tone with durations of around 3, 9, and 18 s and to press the button as quickly as possible as soon as the tone stopped (the control phase). For details concerning the methods, see the Supplementary Information.

In accordance with former studies employing the temporal reproduction method\textsuperscript{24,25}, the mean of the reproduced intervals were accurate for the 3 s standard interval (mean reproduction: 2918 ms, S.D.: 628) and progressively shortened with increasing interval lengths: 7576 ms (S.D. = 1434) for the 9 s interval and 12702 ms (S.D. = 2723) for the 18 s interval (see Fig. S 1).

First, we asked which brain areas are activated during the encoding and reproduction phase for the three different durations. Two-way (task, duration) analyses of variance (ANOVA) were conducted to test the differences of activation for the two contrasts: (1) encoding vs. control phase and (2) reproduction vs. control phase (p < 0.01, corrected). Several brain areas were significantly activated for the contrasts shown separately for the three durations (Supplementary Tables 1, 2). Specifically, the supplementary motor area (SMA) was activated across all durations in the encoding phase. Specifically for the 9 and 18 s intervals, in addition to other areas, activations in posterior insular and superior temporal cortices were found. Relative to the encoding phase, the reproduction of time intervals engaged more
anterior portions of the brain, which is most evident in the anterior shift of medial frontal (partly SMA) activation during the 9 and 18 s intervals (see Fig. 2). Additionally, in the encoding phase only posterior structures of the insular cortex showed significant activation differences, whereas in the reproduction phase activation in the posterior as well as (more pronounced) the anterior insula was observed together with inferior frontal activation.

Our second question focused on the time course of neural activity in the identified brain regions of interest (ROI) for the 9 and 18 s intervals. We found two fundamentally different temporal activation patterns (Fig. 2 A, B): (1) a rapid-onset, steady increase of activation over time or ‘climbing activity’ that peaks at the end of the stimulus (the assumed peak of the hemodynamic function = stimulus length + ca. 6 s delay) and (2) an inverted u-shape activation that increases with a considerable delay after stimulus onset and decreases before the end of the stimulus. A factor analysis conducted over the time courses of activation in the ROI confirms the existence of two different factors corresponding to the two observable temporal activation patterns (see Supplementary Table 3). In the 9 s condition, climbing neuronal activity is detectable in the ROI that encompasses the right-sided posterior insula and portions of the superior temporal and pre-central gyrus (Fig. 2 A). In the 18 s condition, climbing activity is visible for the ROI in the right posterior insula (and parts of the post-central gyrus), the left posterior insula, and a right superior temporal and inferior parietal region (Fig. 2 B). Inverted u-shape functions in the 9 and 18 s conditions are seen for the right pre-central gyrus, the SMA bilaterally (Fig. 2 A, B) and a right pre-post central area. A ROI encompassing the left posterior insula, parts of the pre-post central gyrus as well as superior temporal gyrus displays
characteristics of both types of time activity curves, namely the observed activation increases immediately after stimulus onset and plateaus before dropping shortly before the end of the stimulus (Fig. 2 A).

In the reproduction phase, time activity in different ROI exhibit a similar temporal profile, i.e. show a monotonic rise followed by a sudden drop about two to four seconds before the actual button press (Fig. 2 C, D). This pattern can be seen during the reproduction of the 9 s intervals for the ROI identified to be located in the right SMA (Fig. 2 C), the right post-central, inferior parietal cortices, the left inferior frontal cortex, the right anterior insula, inferior frontal cortex, the right inferior frontal cortex, the left posterior insula. During the reproduction of the 18 s interval this activation pattern emerges only ~10 s before the button press in the ROI in a right medial frontal area, the left anterior insula, and the right anterior insula (Fig. 2 D). Thus, while activity during the encoding phase continues until the termination of the stimulus (presumably to adequately represent its duration), the reproduction phase activity in the ROI peaks 2 to 4 seconds before the motor response (presumably reflecting the moment at which the decision is made as to when to stop the tone).

The time activity curves in the encoding phase are not unlike those recently reported in neurophysiological animal studies showing that specific climbing neuronal activity, interpretable as representing a temporal integrator-like function, encodes short durations\textsuperscript{26, 27}. Neuron ensembles in pre-motor and motor cortex\textsuperscript{28} as well as posterior parietal cortex\textsuperscript{29} of rhesus monkeys monotonically increase (or decrease) their activity throughout delays up to a few seconds before a timed motor response is made. We similarly interpret the bilateral climbing neuronal activity in posterior insula, superior temporal and right inferior parietal gyrus as indication of an
ensemble accumulator process, i.e. the increasing engagement of multiple local neural circuits to encode duration of auditory signals (thus, also the engagement of the superior temporal cortex). Theoretical models have been developed showing how signal accumulation over time can function as a time keeper\textsuperscript{13,21,27}. In contrast, the u-shape function might be involved in attention and working memory processes supportive of the timing task.

The insular cortex is part of the extended limbic system, and is strongly involved in subjective feeling states and interoceptive (within the body) awareness. The posterior insula is specifically implicated as the basic receptive area for visceral input, that is, for physiological states of the body\textsuperscript{9,10}. Activation of the insular cortex has repeatedly been shown during neuroimaging tasks on time perception but its significance has seldom been discussed\textsuperscript{6,8,14}. It is only very recently that a conceptual framework for an anatomical and structural model of insular cortex has been formulated. Craig\textsuperscript{30} suggests that insular cortex integrates interoception and the processing of emotional moments with the perception of time. In line with this proposal we show that the posterior insula is a key neural substrate for the encoding of duration of multiple seconds and that, consequently, the accumulation of physiological changes in body states registered in the posterior insula may contribute to our perception of time.

This is the first study in humans showing an integrator-like neuronal function over time involved in the representation of duration. The finding that neural activity accumulates in the posterior insula provides key evidence for piecing together a theory in which interoception might function as the prime source for our subjective experience of duration of multiple seconds.
METHODS SUMMARY

Functional MRI data was collected while subjects temporally reproduced tone intervals with varying durations of 3 sec, 9 sec, and 18 sec. Each trial started with a 1.2 kHz tone presented for one of the three durations (i.e. the encoding phase). After a short pause a 2 kHz tone (i.e. reproduction phase) was presented (see Fig. 1). This second tone had to be stopped by the subject when she believed that it had reached the length of the first tone. In order to contrast both the encoding and the reproduction phases with the control task phase (see below) subjects had to also press a button as fast as possible at the end of the encoding phase of the timing task. This was implemented in order to have comparable attention and motor preparation demands in all three task phases.

In the control reaction time task subjects listened to 2 kHz tones with variable durations (control phase) and to press the button as quickly as possible as soon as the tone stopped. Unbeknownst to the subject, the tone durations were identical to the reproduced durations in the reproduction task of a previous behavioral session outside the scanner. To prevent subjects from counting, a secondary memory task was employed in both the temporal reproduction and the control task (Fig. 1; see also the Supplementary Material).

Functional ROI were identified for the contrasts between the encoding and the control phase as well as the reproduction and the control phase (p < 0.01, corrected). The time activity curves from these regions were extracted for each participant and averaged over the time points of acquisition (every 2s). Individual time activity curves during the 9 and 18 s encoding phases were normalized (set to zero) at the onset of the standard stimulus. Individual time activity curves for the 9
and 18 s reproduction phases were aligned to the actual individual reproduction times of the participants (stopping the second tone plus the projected delay of the hemodynamic function).

**Full Methods** and any associated references are available in the online version of the paper at www.nature.com/nature.


**Supplementary Information** is linked to the online version of the paper at www.nature.com/nature.

**Acknowledgments** Thanks are due to Jan Churan for his invaluable help in shaping the WinVis for Matlab scripts and to Virginie van Wassenhove for comments on the manuscript. This work is supported by a grant from NIDA (1R03DA020687-01A1 to M.P. and M.W.) and by a grant from the Kavli Institute for Brain and Mind (KIBM 07-33 to M.P. and M.W.).

**Author contributions** M.W., A.N.S., and M.P.P. were responsible for the overall study design. M.W. and J.L.A conducted the behavioral and fMRI experiments. M.W., A.N.S, and M.P.P. analyzed the fMRI data and M.W. wrote the paper with the help of all authors.

**Author Information** Reprints and permissions information is available at www.nature.com/reprints. Correspondence and requests for materials should be addressed to M.W. (wittmann@ucsd.edu).
Figure 1 | Task design: Trial events in the temporal reproduction and the control reaction time task (for details, see Supplementary Information). To discourage subjects from counting (which they were instructed not to), in both the timing and the control task, a secondary memory task had to be performed. In the timing task, subjects first saw for three seconds four numbers on the screen. Then, a continuous 1200 Hz tone was presented for one of three durations (3, 9, 18 seconds). After the tone had stopped subjects had to press a button as fast as possible. After a short pause a continuous 2000 Hz tone was presented that had to be stopped by pressing a button when the subjects thought that it has lasted as long as the first stimulus. Then one single number appeared on the screen and subjects had to decide by pressing one of two buttons whether it was one of the four numbers seen at the beginning of the trial. The control reaction time task was characterized by subjects reacting as fast as possible with a button press when a 1200 Hz tone stopped.

Figure 2 | Brain activity related to the encoding > control (A, B) and reproduction > control contrasts (C, D) (P < 0.01, corrected) are coded by yellow to red voxels (activation) and blue (deactivation) and superimposed on the average of anatomical images of the 14 subjects (sagittal and axial planes). Individual time activity curves during the 9 and 18 s encoding phases were normalized (set to zero) at the onset of the standard stimulus. In the encoding phase climbing brain activity can be discerned that peaks at the end of the stimulus duration (with a delay of ca. 6 seconds reflecting the hemodynamic response function) in the right posterior insula (R p Ins) (9 and 18 sec, A, B, respectively) as well as in the left posterior insula (L p Ins) and the right superior temporal (ST) and inferior parietal (IP) cortex. An inverted u-shape
function is detected in medial frontal (SMA). In the reproduction phase time activity curves in the region of interest (ROI) peaks two to four seconds before the button press (C, D). Among other regions, medial frontal as well as bilateral anterior insula (a Ins) and the inferior frontal (IF) regions show this temporal envelope.
Temporal reproduction task:

- 1200 Hz tone (Encoding phase)
- Reaction time
- Pause
- 2000 Hz tone (Reproduction phase)

Control reaction time task:

- 2000 Hz tone (Control phase)
- Reaction time
- Decision: y/n
A

Encoding phase 9 s

x = 8

z = 14

* projected peak of hemodynamic response
*projected peak of hemodynamic response
C
Reproduction phase 9 s

x = 4

R SMA

R a Ins, IF

L a Ins, IF

z = 2

button press

R SMA

L a Ins, IF

R a Ins, IF
Reproduction phase 18 s

ROI activation

button press

duration [sec]

R medial F

L a Ins

R a Ins, IF

x = 4

z = 2

medial F

R

L

IF

Ins