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## Abstract

Loud acoustic stimuli can unintentionally elicit volitional acts when a person is in a state of readiness to execute them (the StartReact effect). It has been assumed that the same subcortical pathways and brain regions underlie all instances of the StartReact effect. They are proposed to involve the startle reflex pathways and the eliciting mechanism is distinct from other ways in which sound can affect the motor system. We present an integrative review which shows that there is no evidence to support these assumptions. We argue that motor command generation for learned, volitional orofacial, laryngeal and distal limb movements is cortical and the StartReact effect for such movements involves transcortical pathways. In contrast, command generation for saccades, locomotor corrections and postural adjustments is subcortical and subcortical pathways are implicated in the StartReact effect for these cases. We conclude that the StartReact effect is not a special phenomenon mediated by startle reflex pathways, but rather is a particular manifestation of the excitatory effects of intense stimulation on the central nervous system.

**Keywords:** Acoustic stimulation; Cortex, Motor control; Motor cortex; StartReact effect.

## 1. Introduction

Rapid onset, brief sound bursts of moderate to high intensity can have several involuntary effects on the human neuromuscular system. They are eliciting stimuli for various reflexes including the (auditory) startle reflex, the acoustic (stapedius) reflex, the audio-laryngeal and audio-perioral reflexes, and the orienting reflex (see, e.g., Davis, 1984, Gogan, 1970, Margolis and Levine, 1991, Mcclean and Sapir, 1983, Sapir et al., 1983). They have effects

on the excitability of neurons in the spinal cord that are observable as changes in the magnitude of responses evoked from the autogenic stretch reflex pathways (Davis and Beaton, 1968, Paltsev and Elner, 1967, Rossignol and Jones, 1976). These effects on spinal excitability have been observed following stimuli that have insufficient strength to evoke a startle response (Rossignol and Jones, 1976). Rossignol (1975) argues that the effects are mediated by the startle reflex pathways, but there are more recent data to suggest cortical involvement (Liegeois-Chauvel et al., 1989). Associated with the startle and orienting reflexes is the involuntary interruption or disruption of on-going motor behaviour (Blumenthal et al., 2015, Sokolov, 1963, Landis and Hunt, 1939). For example, aiming a rifle at a target and on-going, manual tracking tasks can be seriously disrupted for a few seconds by a loud burst of noise (Foss et al., 1989b, Foss et al., 1989a, Thackray and Touchstone, 1970, Vlasak, 1969), and in some tasks the disrupting effects can persist for as long as 30 seconds (Thackray and Touchstone, 1970, Woodhead, 1958).

The effects mentioned in the previous paragraph are well established and some have been known about for over 100 years (Bowditch and Warren, 1890, Simons, 1996). Within the last twenty years another effect of unexpected, acoustic stimulation on the motor system has been discovered: a startling stimulus can trigger an action that a person is in a state of readiness to perform (Valls-Solé et al., 1999). This has been called the *StartReact* effect (Carlsen et al., 2004b, Valls-Solé et al., 1999) and it has considerable potential as a therapeutic tool in neurological conditions where movement initiation is impaired (see Honeycutt and Perreault, 2012, Rothwell, 2006, Honeycutt and Perreault, 2014, Honeycutt et al., 2015), and as an experimental tool for the study of motor preparation (e.g., Carlsen et al., 2011, Nonnekes et al., 2015).

Most studies of the StartReact effect have utilized a simple reaction time (RT) protocol in which a person is ready to perform an action in response to an imperative stimulus (IS) presented in a non-auditory modality (usually vision). An accessory stimulus is not an IS, rather it is a stimulus that the experimental participant is instructed not to respond to. If the accessory stimulus is a startling acoustic stimulus presented at the same time as the IS, the RT is substantially shorter than the normal voluntary RT to the IS and close to the latency of the startle reflex response (Carlsen et al., 2004b, Valls-Solé et al., 1999).

A popular explanation for the StartReact effect is that it involves involuntary triggering by the accessory loud acoustic stimulus (LAS) rather than by the IS and is mediated by a subcortical mechanism (Carlsen et al., 2004b, Valls-Solé et al., 1999). Someone who has prepared a response is hypothesized to store a motor program for this response in subcortical circuits; the startling stimulus evokes brainstem activity that excites these circuits and releases the stored program (Carlsen et al., 2011, Nonnekes et al., 2014b, Valls-Solé et al., 2008, Valls-Solé et al., 1999). It has been further proposed that the circuitry of the acoustic startle reflex is essential to the triggering process and that evoking a startle response is necessary for the StartReact effect (Carlsen et al., 2011, Maslovat et al., 2015, Valls-Solé et al., 1999). We will refer to this explanation of the effect as the *startle triggering hypothesis*. To summarize the above description, this hypothesis comprises five components: (1) a sudden, loud acoustic stimulus (LAS) can involuntarily evoke (trigger) a prepared voluntary act if presented at the right moment (the StartReact effect). (2) In order for the program to be triggered, the LAS must evoke a startle reaction. (3) The triggering mechanism responsible is implemented by subcortical circuits without involvement of the cerebral cortex. (4) The prepared motor program is stored subcortically. (5) All instances of the StartReact effect involve this same subcortical mechanism (that described in items 3 and 4).

Note that component (1) simply identifies the LAS as the (involuntary) trigger for the response, the other components describe the mechanism that is hypothesized to underlie this triggering process. The startle triggering hypothesis is not universally accepted and several of the components have been a source of controversy, such as the necessity of evoking a startle response (component 2) and the subcortical storage of motor programs (item 4) (see e.g. Alibiglou and MacKinnon, 2012, Marinovic et al., 2013, Nonnekes et al., 2014b, Stevenson et al., 2014, Marinovic et al., 2014c). In this review we evaluate the evidence for each of the five components. We argue that there is substantial evidence that loud acoustic stimuli can involuntarily trigger prepared actions. However, we argue that there is no evidence that provides unequivocal support for the other components. There is no evidence to establish either the necessity or the sufficiency of a startle reaction (component 2), making the term ‘StartReact’ something of a misnomer. Components (3) and (4) together suggest that the StartReact effect is a subcortical phenomenon that operates without cortical involvement. We argue that there is no evidence to suggest that this is the case. Although some behaviours are undoubtedly generated by subcortical mechanisms (or ‘programs’), for others the cortex appears to be essential for their production, notably learned skills involving the orofacial, laryngeal and distal limb musculature. We argue for cortical involvement in the StartReact effect when the response involves learned skills that use this musculature. For other acts that have been claimed to exhibit StartReact effects – including saccadic eye movements and postural reactions – the mechanisms are likely to be entirely subcortical, indicating that the component (5) is not correct. We put forward the hypothesis, which we argue is supported by the available data, that StartReact effects for actions driven by cortically generated motor commands involve quite different neural mechanisms to those driven by subcortically generated commands.

## 2. Component 1: Can a sudden, loud acoustic stimulus involuntarily trigger a prepared action?

It has been known for over 100 years that (voluntary) RTs to combinations of two or more stimuli in different modalities are shorter than the RTs to one of the stimuli presented on its own (e.g., Todd, 1912). In a typical experiment (for variants, see Colonius and Diederich, 2012), a stimulus in one modality is the designated IS and stimuli in one or more other modalities serve as *accessory stimuli* (i.e., not to be volitionally responded to). Accessory stimuli are typically presented at the same time as the IS, though they may be presented up to 500 milliseconds before it or up to 100 ms after it (e.g., Bernstein et al., 1969, Hershenson, 1962, Gielen et al., 1983, Welch and Warren, 1986). A majority of studies have used just one accessory stimulus and the auditory and visual modalities (see, e.g., Diederich, 1995, Gielen et al., 1983). The finding is that when both the IS and accessory stimulus are presented, the voluntary RT is shorter than when the IS is presented alone, regardless of whether the IS is visual or auditory (Nickerson, 1973, Diederich, 1995). This shortening of voluntary RT by accessory stimuli is known as *intersensory facilitation* of RT (Colonius and Diederich, 2012, Todd, 1912).

There are several possible mechanisms that might account for the shortening of RT (Gielen et al., 1983, Nickerson, 1973, Miller, 1982, Raab, 1962). These fall into two basic classes: separate activation (or race) mechanisms and coactivation mechanisms (Colonius and Diederich, 2012). In the former, processing of the two stimuli does not interact – they are processed separately and so there is, in fact, no actual facilitation going on at a mechanistic level. In the latter, processing of the two stimuli does interact – their neural representations are combined or integrated in some way and so there is a form of facilitation at the mechanistic level. The consensus is that a coactivation type mechanism is largely responsible for intersensory facilitation of RT, particularly when the delay between the IS and accessory

stimulus is very short or zero (Diederich and Colonius, 2004, Colonius and Diederich, 2012). Most studies of the StartReact effect have used a RT task in which a visual IS and an accessory LAS are presented essentially simultaneously (e.g., Carlsen et al., 2004a, Valls-Solé et al., 1999), but the startle triggering hypothesis proposes that combination of stimulus activity from the two modalities is not responsible for the RT reduction (a coactivation-type mechanism is not involved). The hypothesis proposes instead that the LAS alone triggers the response. In this respect it is similar to mechanisms of the separate activation type, except that the triggering process is assumed to be involuntary and subcortical, whereas separate activation mechanisms are accounts of reductions in *voluntary* RT (see, e.g., Raab, 1962).

The basic reason for proposing that the StartReact effect is not an instance of intersensory facilitation is the magnitude of the RT reductions involved. RT reductions in intersensory facilitation typically range from 20 to 50 milliseconds (Nickerson, 1973), whereas the StartReact effect involves much greater reductions (from 70 to 90 ms; Valls-Solé et al., 1999) such that the response latency is close to that of the acoustic startle reflex response. The argument is that voluntary responses to stimuli cannot plausibly have such short RTs nor can they plausibly be produced by coactivation type mechanisms that integrate acoustic and visual information (Valls-Solé et al., 2008, Valls-Solé et al., 1999). Thus, the conclusion has been that the StartReact effect is due to an involuntary triggering of a prepared response by the LAS and involves completely different neural mechanisms and pathways to those that underlie intersensory facilitation.

Before it can be firmly concluded that the reductions in RT that characterize the StartReact effect are due to involuntary triggering by a mechanism different to those underlying voluntary responses to stimuli, there is another factor that needs to be excluded as a possible explanation: the high intensity of the accessory stimulus. It has been known since the early 20<sup>th</sup> Century that voluntary RTs to high intensity stimuli are shorter than those to



less intense stimuli (Pieron, 1914, Woodworth, 1938). The RT-intensity relationship is well described by a power law, known as Pieron's Law after its discoverer (Luce, 1986). The large RT reductions characterising the StartReact effect could be the result either of combined intersensory facilitation and stimulus intensity effects, or just the latter. Carlsen et al. (2007) attempted an explicit test of this possibility. They found that when the accessory LAS evoked a startle response, RTs were 20-30 milliseconds shorter than RTs observed when no measurable startle was evoked, and also showed a qualitatively different variation with LAS intensity (see Figure 1). These results support the involvement of a fast, startle-dependent response-triggering mechanism that depends only on the accessory LAS.

As discussed later (section 3), Carlsen et al.'s (2007) results are not completely conclusive, but there are other findings that suggest that responses can be triggered by an accessory LAS. These come from studies in which the LAS is presented before the IS or when the IS is omitted (Carlsen and Mackinnon, 2010, Kumru and Valls-Solé, 2006, MacKinnon et al., 2013, Marinovic et al., 2013, Nonnekes et al., 2013). For example, Marinovic et al. (2013) reported that for accessory LASs presented before the IS, RT measured from LAS onset decreased as the time period between LAS and IS delivery (LAS-IS onset asynchrony) decreased. However, RT measured from the time of IS delivery increased as the LAS-IS onset asynchrony decreased. This pattern of results is expected if the response is triggered by the LAS. If responses were triggered by the IS, the expected pattern of results would have been a reduction in RT latency irrespective of whether RT is measured relative to the LAS or IS onset. In addition, Mackinnon and colleagues (2010) have shown that prepared responses can be elicited by acoustic stimulation occurring more than a second prior to the IS. Not only do these findings demonstrate that the StartReact effect is not an instance of intersensory facilitation, they also demonstrate that the triggering effect is not simply a blending together of a startle response with a slightly longer latency voluntary

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response in the same muscles (additional evidence derives from StartReact effects that occur in the absence of measurable startle responses, discussed in section 3). Evidence against this blending hypothesis originally derived from a failure to find a statistically significant difference between EMG burst durations in StartReact trials and control (no LAS) trials (Valls-Solé et al., 1999). Such evidence is statistically very weak since it relies on confirming the null hypothesis, a situation made worse by the fact that startled RTs come from a very small number of trials per participant.

Thus, it would seem to be reasonably clear that an accessory LAS can trigger a prepared response if it is presented at an appropriate time. This triggering is unintended and occurs when people are explicitly instructed not to respond to the LAS. Response latencies are much shorter than the normal voluntary RT, suggesting that it involves different and faster processes than those involved in the voluntary RT.

### **3. Component 2: Is a startle reaction necessary for triggering by an accessory acoustic stimulus?**

It has been argued that the triggering mechanism responsible for the StartReact effect is only activated by a ‘truly’ startling stimulus (see, e.g., Carlsen et al., 2007, Maslovat et al., 2015). A truly startling stimulus is one that evokes the ‘whole-body’ or ‘generalized’ skeletomotor startle response, whereas a stimulus that evokes only an eye-blink is deemed to be not ‘truly’ startling (Maslovat et al., 2015). Two distinct eye-blink responses can be elicited by rapid onset acoustic stimuli: a short latency response that can occur in the absence of any measurable startle-related activity, and one with a latency about 20 milliseconds longer that is associated with startle responses in other muscles (Brown et al., 1991, Meincke et al., 2002, Rushworth, 1962). The short latency response is thought to be mediated by pathways distinct from those underlying the acoustic startle response in other muscles (Gironell et al., 2003,

Brown et al., 1991), has a lower threshold (is elicited by less intense stimuli) and is more resistant to habituation (Brown et al., 1991, Maschke et al., 2000). Consequently, two reflexes are distinguished: the short latency *acoustic eyeblink reflex*, considered to be an eye-protective reflex (Brown et al., 1991), and the *acoustic startle eyeblink reflex* that is a component of the startle reflex. It is very difficult to determine from orbicularis oculi EMG records whether one or both responses have been elicited (Brown et al., 1991, Meincke et al., 2002), making the orbicularis oculi response unreliable as an indicator of a true startle response. A better indicator would be a response in one of the other muscles involved in the startle response; of the various possibilities, sternocleidomastoid (SCM) is arguably the most appropriate (Brown et al., 1991, Carlsen et al., 2007, Maslovat et al., 2015).

Carlsen et al. (2007) used the SCM EMG startle response index and divided trials in which the LAS elicited a response (SCM+ trials) from trials that did not (SCM-). Figure 1 shows the RTs from these two types of trial for the five different LAS intensities used. The figure shows evidence for two effects: (1) RTs were 20-30 ms shorter in the SCM+ trials than in the SCM- trials (similar to RTs in other reports of the StartReact effect); (2) RTs were shorter when the stimulus was more intense in SCM- trials (as expected from Piéron's Law), but not in SCM+ trials. The first effect was interpreted as due to a fast, involuntary, subcortical triggering mechanism operative when the startle response was evoked (SCM+ trials). The decrease in RT with increased intensity in SCM- trials was interpreted as a reflection of the mechanism, presumably cortical, normally responsible for triggering responses in voluntary RT tasks. Given that very short mean RTs and absence of an intensity effect were only observed for the SCM+ trials, the authors argued that a startle response is necessary for the StartReact effect, and several subsequent studies have supported this interpretation (Carlsen et al., 2009, Honeycutt et al., 2013, Carlsen et al., 2007, Maslovat et al., 2015).

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However, there are at least three difficulties with interpreting the results as evidence that evoking a startle is necessary for the StartReact effect. First, the results in Figure 1 are statistical summaries of the experimental data and do not tell us whether any short premotor RTs characteristic of the StartReact effect (less than 90 ms) occurred in SCM- trials. When premotor RT distributions rather than just means and standard deviations are presented, it is clear that short RTs occur in SCM- trials and long RTs occur in SCM+ trials as shown in Figure 2 (Carlsen et al., 2009, Maslovat et al., 2015), though the proportion of short RTs in SCM- trials is smaller than in SCM+ trials and the proportion of longer ones is smaller in SCM+ trials is smaller than in SCM- trials. In both cases the proportions are very much greater than in control trials (no LAS presented), where almost no RTs under 90 ms are typically recorded (< 1% of control trials in Carlsen et al., 2009). If short RTs occur in SCM- trials, then it cannot be concluded that a startle response is a necessary condition for the StartReact effect. Moreover, if long RTs occur in SCM+ trials, then it cannot be concluded that a startle response is a sufficient condition for the effect.

Second, several studies have failed to find statistically significant differences between RTs in trials with and without SCM activation (Campbell et al., 2013, MacKinnon et al., 2007, Nonnekes et al., 2014a, Reynolds and Day, 2007, Nonnekes et al., 2013, Rogers et al., 2011, Marinovic et al., 2014b) and some have found evidence that the StartReact can occur independently of SCM activation. Using a prepulse inhibition paradigm (Blumenthal, 1996, Hoffman and Ison, 1980), it has been demonstrated that the SCM response can be abolished while leaving the StartReact effect unchanged (Maslovat et al., 2012, Valls-Solé et al., 2005, Lipp et al., 2006).

Third and last, the different shapes of the graphs for SCM+ and SCM- trials in Figure 1 (flat and a downward trend with increasing intensity, respectively) are consistent with a difference in the triggering mechanisms involved, but that is not the only possible interpretation. Another possibility is that the triggering mechanisms are the same, but that there is a lower limit to the RT of around 70 milliseconds (a floor), and in the SCM+ trials a larger proportion of the RTs are at this floor.

As a final point, it should be noted that a failure to observe a detectable EMG response in SCM is not a conclusive demonstration that a true startle response did not occur. Any conclusions drawn from differences between SCM+ and SCM- trials inherit this inconclusiveness. It stems from two sources: (1) the method used to determine SCM activation, (2) different effects of loud sounds on SCM activity. Surface EMG has been used to detect SCM activity in StartReact studies with the occurrence of a response identified using a multiple of the standard deviation (SD) of baseline activity as a criterion (typically  $>2SD$  above baseline, e.g., Carlsen et al., 2009). This method rejects any SCM responses less than the criterion and is likely to be relatively insensitive to activity in SCM motor units that are distant from the recording electrodes (De Luca, 1997). In primates the SCM is a compartmentalized muscle with superficial and deep compartments (McLoon, 1998): it is possible that if only a few deep compartment motor units are activated, the response recorded from surface EMG electrodes would not reach criterion and so be classed as SCM-. In relation to the second difficulty, intense sounds are capable of evoking responses in SCM motoneurons as a result of incidental vestibular stimulation (Murofushi et al., 1999, Rosengren et al., 2010, Todd, 2001), which appears to be a manifestation of the sacculocollic reflex (Rosengren et al., 2010, Wu et al., 1999). The effect on SCM motoneurons is initially inhibitory as the sacculocollic reflex pathway bilaterally inhibits SCM motoneuron pools (Uchino et al., 1997, Wu et al., 1999). Thus, if a loud sound elicits near simultaneous

excitatory startle and (small) inhibitory sacculocollic reflex responses in SCM, the recorded response could be too small to detect, despite a startle reflex being elicited.

A question remains, of course, regarding why RTs less than 90 milliseconds are more likely when SCM activation is recorded, irrespective of the stimulus intensity (at least for intensities greater than 93 dBa). The mechanism underlying this association between SCM activity and greater StartReact probability may be more or less 'direct'. If the mechanism is direct, then activation of the startle pathways is not only responsible for evoking an SCM response, but these pathways are also the route (or a significant component thereof) by which LAS evoked activity is transmitted to the motor program circuits so as to 'release' the prepared response commands. In other words, activity in the startle pathways plays a causal role in triggering the response. If the mechanism is indirect, then activation in the startle pathways plays no causal role in triggering the response. In this case, another factor is at work that increases the excitability of reflex pathways and other pathways, including those that transmit LAS evoked activity to the motor program circuits. We have argued that this additional factor is the state of preparation for voluntary action (Marinovic et al., 2015a) as it has long been established that preparatory state can increase reflex excitability, including startle reflex excitability (see, e.g., Brunia, 1993, Valls-Solé et al., 1995, Bohlin and Graham, 1977). According to this idea, when the level of motor preparation is high, a LAS is both more likely to evoke a measurable startle response and more likely to trigger the prepared response, but the pathways involved are different. Consistent with this idea, Mackinnon et al. (2013) reported that incidence of triggering of responses was correlated with electroencephalographic indices of cortical motor preparation. The role of motor preparation is discussed in more detail in section 6.

Overall, there is no conclusive evidence that a startle response is either necessary or sufficient for the StartReact effect. Indeed, the evidence that it is not necessary is arguably more convincing since there are clear demonstrations of RTs in the StartReact effect range occurring in the absence of a measurable startle response. Cases where a higher probability of the StartReact effect is associated with SCM activation can be interpreted as a result of the facilitating effects of motor preparation on reflex pathways: the motor program circuits have a higher level of preparatory activation and the reflex circuits are more excitable, so the LAS is both more likely to elicit a startle response and to trigger the prepared act. That a startle response is not necessary for the StartReact effect is also consistent with reports which demonstrate triggering of a prepared response by non-auditory, non-startling accessory stimuli (Fink et al., 2009).

#### **4. Component 3: Do the experimental data exclude a role for the cerebral cortex in triggering?**

The third component is the assertion that the triggering process is subcortical and the cortex plays no role in the StartReact effect (Maslovat et al., 2015, Valls-Solé et al., 1999, Valls-Solé et al., 1995). Together with the proposal that prepared motor programs are stored subcortically (component 4), the idea is that that the StartReact effect is an entirely subcortical phenomenon. Although subcortical triggering and program implementation are two necessary parts of this idea, we discuss them separately because it could be that programs are subcortical, but that triggering them involves a transcortical pathway. In this section we consider the arguments for and against the possibility that the triggering pathway involved is transcortical. In sections 5 and 6 we consider the nature of motor programs and the locus of the circuits that implement them.

The proposal that the pathways involved in triggering are subcortical rather than transcortical was originally based on the latency of the evoked potentials in auditory cortex that reflect the cortical response to the first volley of action potentials from the thalamus (middle latency potentials). Valls-Solé and colleagues assumed a latency of about 35 ms (Erwin and Buchwald, 1986, Valls-Solé et al., 1999). If the StartReact effect involved a transcortical pathway, then for an upper limb response it would take at least another 15-25 milliseconds for commands to be transmitted to the muscles and be detectable in the EMG (Fuhr et al., 1991). Thus, transmission of a sensory signal to auditory cortex and transmission of the command to the muscles accounts for at least 50-60 milliseconds of the (premotor) RT. Since the premotor RT averaged about 77 ms and could be as short as 65 ms in Valls-Solé et al.'s (1999) study, there would only be between about 5 ms and 27 ms for processing sensory stimuli, making a decision and transmission between cortical areas, which is unfeasibly little time (Valls-Solé et al., 1999).

The above argument depends upon the estimate of middle latency auditory potentials assumed by Valls-Solé and colleagues. This estimate is too long as several studies have shown that the latency of these potentials can be as short as 11 ms (Kuriki et al., 1995, Godey et al., 2001). Such a latency is compatible with transmission from the cochlea to the auditory cortex via the trisynaptic components of the classical auditory pathway (see Moller, 2003, Hackett and Kaas, 2003). Thus, the amount of time available for processes intervening between arrival of stimulus activity in auditory cortex and production of descending signals increases from 5-27 ms to 30-52 ms, a range compatible with a transcortical pathway. It is also possible that stimulus evoked activity does not reach the cortical areas responsible for descending signals via the auditory cortex, but by a more direct and hence faster route (Alibiglou and MacKinnon, 2012). Such a route is provided by the pathway that transmits auditory activity via the pontomedullary reticular formation and the thalamus (Koch et al.,



1992, Lingenhohl and Friauf, 1992, Lingenhohl and Friauf, 1994, Davis et al., 1982) to sensorimotor areas of the cortex (Samuels and Szabadi, 2008, Liang et al., 2013). The two possible routes by which auditory signals could be transmitted to motor cortical areas are shown in Figure 3, both are compatible with the short RTs of the StartReact effect.

If a transcortical pathway is involved, the most plausible origin for the descending signals are those areas that give rise to the pyramidal tracts, the most important of which is M1. These signals would either be motor commands (if motor programs are cortical) or trigger signals for subcortical programs (discussion of which of these two possibilities is more plausible is presented in section 6). One reason for doubting that signals from motor cortex are involved in the StartReact effect derives from the finding that a loud auditory stimulus can suppress motor cortical excitability (Ilic et al., 2011, Kuhn et al., 2004, Fisher et al., 2004, Furubayashi et al., 2000). Suppression of the motor cortex would be expected to increase RTs if it is a component of a transcortical pathway and hence these findings provide support for a subcortical triggering mechanism that bypasses motor cortex (Valls-Solé, 2012). However, there are other data to suggest that the effect of the LAS depends upon the task context at the time the stimulus is presented. Using transcranial magnetic stimulation (TMS), we found that the effects depend on the preparatory state of motor system prior to an anticipated action (Marinovic et al., 2014c); see also (Marinovic et al., 2015b): during preparation for a movement, the effect of acoustic stimulation in motor cortical areas was found to be *excitatory* rather than inhibitory. This excitatory effect occurred in exactly the circumstances in which the StartReact effect is observed. In contrast, the suppressive effects were observed in circumstances in which suppression or interruption of behaviour have been reported (people were engaged in an on-going task of maintaining a contraction of the index finger flexors). Thus, the overall pattern of results is consistent with the effects of loud

auditory stimulation described in the introduction: such stimuli tend to interrupt (suppress) on-going behaviour and to trigger prepared actions when a person is in a state of readiness to respond.

Another possible way to assess the involvement of a transcortical pathway is to study patient groups with damage to relevant cortical regions (Honeycutt and Perreault, 2012, Nonnekes et al., 2014b). Honeycutt and colleagues studied chronic stroke patients who suffered significant impairment of voluntary movement due to damage to motor cortical areas. They found that StartReact effects could be unaffected by such damage, which casts doubt on the idea that a transcortical pathway is involved (Honeycutt and Perreault, 2012). However, these findings do not provide a compelling case against a transcortical pathway because the patients had chronic conditions. In such conditions, it is known that the nervous systems can adapt by utilizing different brain regions and pathways to those involved when the nervous system is intact, a problem that has long been recognized as an issue in interpreting deficits in chronic patient groups (e.g., Latash and Anson, 1996). As there is dense interconnectivity between cortex and subcortical structures involving several areas outside M1, there are many possibilities for re-routing motor commands.

A few studies have attempted to test for cortical involvement in the StartReact effect using TMS. Alibiglou and MacKinnon (2012) (see also (Stevenson et al., 2014) demonstrated that supra-threshold, single-pulse TMS over the primary motor cortex reduced the StartReact effect (increased RTs). TMS of this kind is known to increase RT only when delivered over the hemisphere contralateral to the responding limb (Ziemann et al., 1997), which led Alibiglou and MacKinnon (2012) to conclude that the StartReact effect involved a transcortical pathway. Unfortunately, the results are not conclusive (see e.g., Honeycutt et al., 2013) due to finding that suprathreshold TMS is able to interfere with normal activity in the reticular formation in primates (Fisher et al., 2012). If present in humans, similar interference

could explain the increase in RT observed by Alibiglou and MacKinnon if the StartReact effect were mediated by a subcortical pathway involving the reticular formation, as proposed by the startle triggering hypothesis (e.g., Valls-Solé et al., 2008).

Overall, the data from studies of the StartReact effect cannot rule in or out cortical involvement in the phenomenon. The magnitudes of the RTs of triggered responses and the effects of acoustic stimuli on motor cortical excitability are consistent with a transcortical triggering pathway. Of course, this is not evidence for cortical involvement, it only shows that the cortex could be involved.

#### **5. Component 4, part 1: Are programs for prepared actions stored subcortically?**

The idea is that a ‘program’ for generating commands for the effectors is prepared in advance and then stored in a kind of short term memory or buffer (Rosenbaum, 2009, Schmidt, 1982) that is located in subcortical circuits. A program is some kind of instruction set that can be delivered to lower level mechanisms that carry out the instructions. These could be muscle commands that tell each muscle involved in the response how much to contract (or relax) (see e.g., Brooks, 1986, Keele, 1968) or they could be more abstract (e.g., Schmidt and Lee, 2011, Keele et al., 1990): for example, the minimum jerk hypothesis for movement trajectory formation can be formulated as follows, “[the] CNS computes a minimum jerk trajectory ... stores this trajectory somewhere and plays it out like a tape. At each instant of time, the tape provides the desired state of the limb – its location, velocity and acceleration” (Shadmehr and Wise, 2005), p. 353).

A basic problem with the notion that a motor program is a stored set of commands is that there is no empirical evidence that any such process is implemented in any known nervous system and there are no good reasons for supposing that a buffering mechanism serves any necessary purpose in motor control (for a tutorial review see Tresilian, 2012),

chapter 11). There are certainly data that can be interpreted in terms of this conception of the motor program, but although it is appropriate for digital computers, the lack of evidence makes it a controversial notion in biological motor control (see, e.g., Turvey, 2009, Summers and Anson, 2009). In contrast, there is extensive and very good empirical evidence that many behaviours are generated by mechanisms that are known not to be interpretable as programs in the sense of a set of stored commands, including locomotion, coughs, swallows and saccadic eye movements (see, e.g., Grillner, 1985, Grillner, 2003, Kiehn, 2006, Robinson, 1975, Sparks, 2002). The mechanisms involved continuously generate commands as an act unfolds in real time and are often referred to as *central pattern generators* (CPGs) for this reason (Grillner, 2003). In recent decades, the CPGs for saccadic eye-movements – usually called *burst generators* (Scudder et al., 2002) – have been the inspiration for models of the command generating processes for skills like reaching, grasping and speaking (Bullock et al., 1998, Bullock and Grossberg, 1988, Guenther, 1995, Shadmehr and Wise, 2005, Tourville and Guenther, 2011).

The subcortical storage hypothesis can be adapted to the pattern generation conception of motor programs simply by proposing that the CPGs for voluntary actions are implemented subcortically. It is known that in many animal species, including primates, the CPGs for a wide variety of fundamental, ‘instinctive’ behaviours are implemented in subcortical circuits. These include rhythmic behaviours like locomotion, chewing and grooming (e.g., Fentress, 1983, Grillner, 1985, Kiehn, 2006), discrete behaviours such as coughs, swallows, sneezes, withdrawals and saccades (Jean, 2001, Schouenborg, 2008, Sparks, 2002), and behaviours involving sequences such as threat displays and attack, predation, sexual behaviour (including courtship displays), and some foraging activities (see e.g., Bjursten et al., 1976, Flynn, 1972, Grillner, 2003, Grillner, 2006, Pfaff, 1999). Many, if not all, of these CPGs can be triggered into command production by signals produced within

the CNS (see, e.g., Drew et al., 2004, Schall, 2002, Takakusaki, 2008). For example, signals generated within the prefrontal cortex of primates are transmitted to the brainstem saccadic burst generators via the superior colliculi and evoke saccadic eye movements (Helminski and Segraves, 2003, Leichnetz et al., 1981, Schall, 2002). Essentially the same mechanism exists in the human brain and saccades evoked by cortically generated signals are typically referred to as *voluntary* (McDowell et al., 2008). We can voluntarily produce other acts governed by subcortical CPGs such as coughs, swallows, withdrawal and locomotion via signals from cortical areas (Grillner, 2003, Jordan et al., 2008).

Recent results suggest that reaching actions could also involve subcortical pattern generators. Reticulospinal and tectospinal connections have been implicated in these actions (Davidson et al., 2007, Alstermark and Isa, 2012) and activity in the superior colliculi correlated with reaching movements has been reported in monkeys (Werner et al., 1997) and humans (Linzenbold and Himmelbach, 2012). That such activity plays a causal role in the production of reaching movements is evidenced by the finding that reach-like movements can be evoked by microstimulation of the superior colliculi (Philipp and Hoffmann, 2014). There are corticotectal projections that play a role in the control of reaching actions in monkeys (Borra et al., 2010, Borra et al., 2014), making it plausible to suggest that the control of these actions in humans and other primates could be organised similarly to saccadic eye movements, with subcortical pattern generators under the control of specialized cortical regions (see also Day and Brown, 2001).

In summary, the subcortical storage hypothesis can be reinterpreted in terms of pattern generation and there is substantial evidence that the basic, unlearned motor repertoire is mediated by subcortical mechanisms that can be recruited volitionally by activity transmitted from the cerebral cortex. Could a similar organization underlie learned voluntary acts? This question is addressed in the next section.

## **6. Component 4, part 2: Is pattern generation for learned actions implemented subcortically?**

A traditional view has been that many of the axons that make up the pyramidal tracts transmit voluntary motor commands from cortex to motor neuron pools, but if command generation is subcortical, then these tracts must be transmitting some other kind of information. One alternative role for motor cortex is that it is important for learning rather than the production of behaviour. It is known that motor areas of the cerebral cortex in rodents are important in the acquisition, but not the ‘implementation’ of learned behavioural changes including instrumental modifications of reflexes (e.g., Wolpaw, 2007) and the novel sequencing of innate behaviours (Kawai et al., 2015). In these cases, the cortex appears to play what has been described as a ‘tutor’ role in organizing subcortical mechanisms (CPGs and reflex circuits) to better fit the demands of the environment (e.g., Kawai et al., 2015). It has long been supposed that the cortex might play a similar role in the human motor skill acquisition (see Ashby et al., 2010).

An established principle is that human skill acquisition involves a transition from cognitive control in novices to independence from cognition in experts (e.g., Bryan and Harter, 1897, Fitts and Posner, 1967, Snoddy, 1926). Expert performance differs from that of novices in speed (experts are faster), fluency (experts make fewer errors of sequencing, movements are more graceful with smoother transitions between components), temporal structure (in multicomponent skills, experts perform with a distinct temporal rhythm that is lacking in novices), and resistance to interference from concurrently executed cognitive tasks (see Ivry, 1996). These changes are thought to reflect the development of a motor program at a ‘sub-cognitive’ level; control by such a sub-cognitive program is referred to as *automatic* (e.g., Moors and De Houwer, 2006, Fitts and Posner, 1967).

The transition from cognitive to automatic control has been associated with a transfer from cortical to subcortical structures, such as the basal ganglia (e.g., Doyon et al., 2009, Yin and Knowlton, 2006). As Ashby et al. (2010) express it, “novel behaviours are mediated primarily in cortex ... and development of automaticity is a process of transferring control to subcortical structures” (p. 208). Implicit in this proposal is the notion that cortical processing is slow, conscious and ‘cognitive’, whereas subcortical processing is fast, subconscious and automatic. However, it is known that fast, subconscious sensorimotor processes can occur in cortex (e.g., Desmurget et al., 1999, Milner and Goodale, 2006). The proposal that control is transferred from cortical to subcortical structures as learning proceeds suggests that there should be a corresponding decrease in the activity of cortical areas. However, many neuroimaging studies in humans and neurophysiological studies in animals have found that as skill acquisition proceeds, cortical activity increases in some tasks, but in others it decreases or shows redistribution of activity with increases in some areas and decreases in others (see Ashby et al., 2010). Reductions and/or redistribution of activity are what would be expected if the cerebral cortex plays an essential role in well-learned skills as well as in the early stages of acquisition. The early stages of skill learning demand conscious attention but this declines as learning progresses (Fitts and Posner, 1967): such a reduction in attentional demand leads to reduced activity in the attentional networks of the cortex but is accompanied by an increased activity in those areas associated with skill (cf. Wu et al., 2008).

There is also evidence that during learning, subcortical structures – the striatum, in particular – could act in a ‘tutor’ role for the cerebral cortex and establish the cortical connectivity underlying skilled behaviour (see Ashby et al., 2007, Ashby et al., 2010). It is well-established that the striatum is particularly important during the initial stages of skill learning (Packard and Knowlton, 2002), but is not so important in later stages or for retention (Ashby et al., 2010, Desmurget and Turner, 2010), with the exception of some learned

behavioural sequences (e.g., Miyachi et al., 2002). That the striatum is implicated in learned sequences is consistent with its essential role in controlling the tonic inhibition of brainstem and spinal motor pattern generators by the output structures of the basal ganglia (Grillner et al., 2013). This inhibitory drive must be reduced in order to recruit subcortical pattern generators and appropriate temporal control and targeting of the reduction would seem necessary for effective performance of sequences. Given the extensive, direct projections from frontal motor cortical areas to the striatum (Kelly and Strick, 2004) and persistent activity in these areas during performance of well-learned sequences, it seems likely that the control exerted by the striatum also involves the cortex (cf. Ashby et al., 2010).

Studies of the neural mechanisms of skill learning do not provide clear support for the traditional view of a transfer of control to subcortical structures, but rather that well-learned skills are mediated by circuits that involve both cortical and subcortical regions. Of course, this does not tell us from where the motor commands for such skills originate: even if retention and execution of learned skills involve essential contributions from cortical areas, it is possible that the commands themselves are generated subcortically. For example, if a learned skill involved exploitation of subcortical pattern generators recruited in a new sequential or concurrent fashion, then the role of cortex would be in controlling the recruitment pattern and not in generating the commands themselves. However, such cases have not been studied using the StartReact protocol, where the focus has been on discrete volitional acts, often involving the distal musculature of the upper or lower limbs (Carlsen et al., 2004a, Carlsen et al., 2009, Carlsen et al., 2007, Carlsen and Mackinnon, 2010, Landis and Hunt, 1939, Kumru and Valls-Solé, 2006, Nonnekes et al., 2014b, Marinovic et al., 2014a, Lipp et al., 2006) and in two cases, the facial musculature (Marinovic et al., 2014b, Stevenson et al., 2014).



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There is also strong experimental and clinical evidence to suggest that cortical projections to motor neurons and to segmental and propriospinal interneurons play a direct role in motor control, presumably transmitting voluntary motor commands. It has been shown, for example, that the ability to selectively activate individual muscles and joints of the upper limb depends upon the integrity of the corticospinal system (Hoffman and Strick, 1995, Lang and Schieber, 2004). A voluntary command transmission role is particularly compelling for direct corticomotorneuronal connections, which are most prevalent in the orofacial muscles, laryngeal muscles, and the distal musculature of the limbs (e.g., Iwatsubo et al., 1990, Kuypers, 1958, Lemon, 2008, Simonyan, 2014) and have been found to be present only in humans and other primates (Lemon, 2008, Porter and Lemon, 1995). These facts regarding direct corticomotorneuronal connections have led to the proposal that the cortex plays the major role in generating the commands for controlling the muscles in fine manipulative skills involving the hands and in skills that involve the orofacial and/or laryngeal muscles such as speech, singing, whistling and playing wind instruments (see Porter and Lemon, 1995, Martin, 2005, Simonyan and Horwitz, 2011). Although the nature of the command information transmitted from the cortex to the motorneurons has yet to be established (see, e.g., Adams et al., 2013, Raptis et al., 2010, Scott, 2008), there is a general agreement that the signals are responsible for muscular control in fine manipulative and vocal skills.

In summary, the available evidence suggests that the cortex plays a role in the control of many well-learned skills. In some cases, the commands that drive the motorneurons may be generated by subcortical CPGs, but the cortex is involved in establishing their pattern of recruitment. In the case of fine motor skills and control of single joints or muscles, motor cortical areas appear to be the source of the commands themselves. It is important to note that many studies of the StartReact effect have employed responses involving the distal musculature or single degree of freedom limb movements, exactly the kinds of responses that

are likely to involve cortical command generation. There are some exceptions, which opens up the possibility that there could be different neural pathways underlying different StartReact effects, as discussed next.

### **7. Component 5: Does the same mechanism underlie all StartReact effects?**

The foregoing discussion has highlighted the distinction between behaviours (or components thereof) that are driven by subcortical CPGs and a class of learned behaviours that are governed by cortically generated commands. If the StartReact effect is obtained for both types of behaviour, then different mechanisms for the effect may be implicated. Consider first the case when command generation is cortical. The activity that is derived from the accessory stimulus would need to reach the cortical regions responsible if it is to trigger the response. For the case of acoustic accessory stimuli, this could occur by either of the routes shown in Figure 3. As described in section 2, stimulus evoked activity can reach the motor areas of the cerebral cortex sufficiently quickly to evoke responses with RTs in the range associated with the StartReact effect. We have suggested that the important mediating factor is the state of preparatory excitability in (or activation of) motor command generators, which is assumed to increase monotonically to a peak level at around the anticipated time of response initiation (Marinovic et al., 2013, Tresilian and Plooy, 2006). The increase in preparatory excitability is sometimes referred to as *temporal preparation* or *non-specific preparation* and was originally introduced to explain a variety of findings obtained in studies of RT (see Leuthold et al., 2004, Los and van den Heuvel, 2001, Requin et al., 1991). According to the hypothesis we have put forward, command generation is triggered when the activation level of the response command generator exceeds a threshold (Marinovic et al., 2013, Tresilian and Plooy, 2006). In a RT task, this normally occurs when activity derived from the IS (a ‘go’ signal) reaches the command generator. When an accessory stimulus is presented, triggering may occur due

to a combination of activity from the IS and the accessory stimulus (a form of intersensory facilitation). Alternatively, if the accessory stimulus is strong enough and its evoked activity reaches the command generator earlier than IS activity, activity from the accessory stimulus alone can involuntarily trigger the response – a StartReact effect (it could also be considered a special case of statistical facilitation, Raab, 1962). An implication is that an accessory stimulus will be more likely to trigger a response when the level of preparatory excitability is higher and when the stimulus-evoked activity transmitted to the motor system is greater (see Tresilian and Plooy, 2006).

According to this idea, how an accessory stimulus contributes to triggering and to RT shortening depends upon its strength and its timing. If the accessory stimulus is too weak to trigger the response on its own or is too late, then it can only contribute by a coactivation type of intersensory facilitation (adding to activation evoked by the IS). If the stimulus is sufficiently strong and not too late, it can trigger the response in the absence of the IS. Although the route by which activity evoked by an acoustic accessory stimulus reaches motor cortical areas is not established, results show that a LAS can affect motor cortex (Alibiglou and MacKinnon, 2012, Marinovic et al., 2014c, Marinovic et al., 2015b) indicating that the kind of effects proposed in this model are consistent with available data (see section 3). However, not all studies involving distal upper limb musculature have reported finding StartReact effects. Importantly, Carlsen et al. (2009) concluded that StartReact effects cannot be evoked from the distal musculature of the upper limbs and hence, by extension, that there are no cortically mediated StartReact effects.

Carlsen et al.'s (2009) conclusions are based on the data in Figure 4 obtained in two simple RT tasks. Statistical analysis revealed no significant difference between mean RTs in the SCM+ and SCM- trials for the distal task, whereas mean SCM+ RTs were significantly shorter in the proximal task. Thus, the conclusions are based on confirmation of the null

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hypothesis in the distal task. Not only that, but the distal response (index finger abduction sufficient to raise the finger tip from a switch) and the proximal response (20° elbow extension) are clearly not equivalent. This is a weak empirical basis from which to assert the non-existence of cortically mediated StartReact effects, but the data shown in Figure 4 certainly do suggest that the two tasks differed in how RTs were affected by loud acoustic stimuli. The RT distributions were very similar for the two tasks in control trials (82dB acoustic IS, not shown in Figure 4), but in the LAS trials shown in Figure 4 (115dB acoustic IS) they can be seen to differ in two ways. First, the SCM+ and SCM- distributions are distinctly right skewed in the distal task, but less so in the proximal task. Second, the distributions are very similar in the distal task, whereas the SCM+ distribution is shifted towards shorter RTs in the proximal task. This pattern could arise in the following way: due to irreducible conduction delays in the CNS, RTs cannot be any shorter than a certain minimum which will in the order of 10 milliseconds greater for the distal task because the conduction distance is about 50 cm longer. The figure suggests a minimum RT of around 60 milliseconds for the proximal task and between 70 and 80 ms for the distal task. In the proximal task only SCM+ trials have RTs close to the lower limit, whereas in the distal task both SCM+ and SCM- trials do. This indicates that in the distal task (but not the proximal) a relatively large proportion of RTs in response to the LAS are close to the lower limit, leading to right skewed distributions in which differences between trial types are too small to detect. In short, Carlsen et al.'s (2009) data do not demonstrate that StartReact effects cannot be elicited from distal limb muscles. Given that there are other data showing that StartReact effects can be elicited when the response is a hand, wrist or orofacial movement (Kumru et al., 2006, Stevenson et al., 2014, Honeycutt et al., 2013), we conclude that cortically-mediated StartReact effects are possible.

The StartReact effect has also been reported for behaviours driven by subcortically generated commands, including saccadic eye movements (Castellote et al., 2007) and anticipatory postural adjustments (Delval et al., 2012, MacKinnon et al., 2007). The case of anticipatory postural adjustments is different from that of the other types of the response that have been studied in that these adjustments are not volitional, rather they occur as automatic components of volitional acts such as raising a leg (Tonolli et al., 2000), taking a step or moving an arm (Cordo and Nashner, 1982, Horak and Macpherson, 1996). Thus, there are two types of subcortically generated acts that can be triggered by accessory acoustic stimuli: volitionally prepared acts like saccades and involuntary adjustments to or in advance of prepared acts. It is possible that the neural mechanisms underlying the StartReact effect in these two cases differ.

Consider first anticipatory and corrective adjustments. StartReact effects have been reported for anticipatory postural adjustments (Delval et al., 2012, MacKinnon et al., 2007) and corrective adjustments to stepping (Queralt et al., 2008, Reynolds and Day, 2007). There is substantial evidence that such adjustments are generated subcortically (for review see Nonnekes et al., 2015) and they are not normally evoked as reflexive responses to acoustic stimuli. It seems reasonable to infer that StartReact effects for such acts involve wholly subcortical pathways and mechanisms; it would be speculative and implausible to suppose that a transcortical pathway mediates these effects. Thus, StartReact effects for anticipatory and corrective adjustments are likely cases of the release of subcortically generated command sequences in the manner proposed in the original account of the StartReact effect (Valls-Solé et al., 1999, Valls-Solé et al., 2008).

As already noted, the corrective and anticipatory adjustments that can be evoked by accessory acoustic stimuli cannot be directly evoked by voluntary command. Saccades are different since the driving motor commands are produced by brainstem CPGs that can be

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activated volitionally. However, acoustic stimuli can reflexively elicit saccades as components of the orienting reflex response (Sokolov, 1963). Thus, saccades triggered by such stimuli may be specific cases of the orienting reflex rather than examples of the StartReact effect. Since head turns are also components of the orienting response, a similar difficulty arises when interpreting head turns evoked by accessory acoustic stimuli (Siegmund et al., 2001). In order to conclude that short RT saccades or head turns in the presence of accessory acoustic stimuli are instances of the StartReact effect, it is necessary to exclude the possibility that they simply represent orienting reflex responses.

One reason for regarding the left/right saccades and head turns with short RTs reported by Castellote et al. (2007) and Siegmund et al. (2001) as StartReact effects rather than orienting responses is that the sound was equal in the two ears: such stimuli would not normally be expected to evoke an orienting response involving horizontal saccades or head turns since such binaural stimulation signals that the sound source lies in the mid-sagittal plane of the head. However, the fact that participants in the experiments were expecting to make a left/right saccade or head turn in response to an IS, the interpretation is not so clear cut. Consider saccades: preparation for the response in the voluntary RT task involves specifying a target for the saccade through activation of motor maps in the superior colliculi (Schall, 2002, Sparks, 2002). When the saccadic system is activated by an acoustic stimulus via orienting reflex pathways, it is possible that target-related activation of the superior colliculi in readiness for the voluntary response contributes not only to the likelihood that the accessory stimulus will evoke a reflexive response, but also to the characteristics of that response. Thus, it is possible that the saccade is reflexively evoked and shaped by the voluntary preparation.

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An account of this kind just described could be proposed for any subcortically generated response type that is reflexively elicitable by a sudden onset acoustic stimulus of sufficient intensity. If this is what is happening, then the triggering mechanism is simply the normal reflex elicitation process and a special term for it (i.e., StartReact effect) is neither necessary nor useful. In order to establish the existence of true StartReact effects for voluntary acts that are subcortically generated, it is necessary either to empirically demonstrate that the orienting reflex account is incorrect or demonstrate StartReact effects for subcortically generated acts that are not normally elicited by acoustic stimuli. An example would be coughs: coughs can be produced voluntarily or reflexively, but a LAS is not an eliciting stimulus for reflex coughs. Unfortunately, there are no extant data that directly address whether a StartReact effect occurs for such behaviours.

In summary, there are three types of behaviour that have been claimed to be susceptible to StartReact effects: (1) volitional acts involving single joint and/or distal musculature that are generally regarded as being driven by cortically generated commands; (2) volitional acts driven by subcortically generated commands; (3) involuntary, subcortically generated reactions that act to preserve upright posture or adjust the gait cycle. Of these three types, only data relating to (1) and (3) provide unequivocal examples of StartReact effects. The available data are consistent with different neural pathways underlying triggering in these two cases: a transcortical pathway when the commands are cortically generated (see section 3) and subcortical pathway(s) when the commands are generated subcortically.

## **8. Conclusions: Is the StartReact effect special or just a special case?**

The underlying mechanisms of the StartReact effect – involuntary triggering of prepared acts by a sudden onset, loud acoustic stimulus (LAS) – are uncertain and have been much debated. The startle triggering hypothesis asserts that it is not to be explained in terms of

previously described mechanisms by which sounds can affect sensorimotor systems, such as increased reflex and corticospinal system excitability, intersensory facilitation, stimulus intensity effects on RT, or a blending of startle reflex response with voluntary action. The hypothesis makes five component assertions and the case for each was considered. Of these, we conclude that only the first – the effect is due to involuntary triggering of a prepared response by the accessory stimulus – is supported by the available data.

The second assertion – eliciting a true startle response is essential – is not supported as there is no evidence that such a response is either necessary or sufficient for the effect. The third assertion – the triggering process is subcortical – is based largely on arguments that the RTs are too short to involve cortex; we showed that such arguments are ill-founded and that there is no evidence to demonstrate that the cortex is not involved. The fourth assertion – that motor commands are subcortically generated – is more complex: we argue that there are examples of StartReact effects in which commands are likely to be subcortically generated (anticipatory postural responses and corrective responses to stepping) and examples in which commands are likely to be cortically generated (when the ability to perform the response is acquired through learning and involves the orofacial and laryngeal musculature or when it involves single degree of freedom movements of the distal joints of the upper limb). Based on this, it follows that the fifth assertion – that all StartReact effects involve the same mechanism – is false as some StartReact effects involve cortical mechanisms, but others do not.

Based on the foregoing conclusions, we propose that there are at least two neural pathways that can mediate StartReact effects: (1) a transcortical pathway for responses driven by cortically generated commands, and (2) a subcortical pathway for responses driven by subcortically generated commands. Subcortically generated responses include acts such as coughs, swallows and saccades that can be produced volitionally, and acts that are not



normally volitional including adjustments or corrections to postural equilibrium and locomotion. StartReact effects have only been unequivocally demonstrated for the latter type of response. If StartReact effects were clearly demonstrated for the former type (voluntary acts involving subcortically generated commands), the pathway(s) involved could be different from those mediating the effect for corrective and anticipatory adjustments.

This proposal is consistent with the relevant anatomy of the motor system as shown schematically in Figure 5. The figure presents in block diagram form the main regions and structures of the brain that have been discussed, together with descending motor pathways and pathways that conduct activity evoked by auditory stimulation and so could serve as mediating routes for StartReact effects. Acoustic stimuli evoke activity in the primary sensory neurons of the cochlear nuclei and this is transmitted via several pathways directly to various brainstem structures (shown in green): the superior olivary complex (SOC), the inferior colliculi (IC) and to various locations in the pons and medulla (Cant and Benson, 2003). From the inferior colliculi, auditory-related activity can reach the cortex (via the thalamus), the superior colliculi and most of the other brainstem structures (including the cerebellum, which is not shown in Figure 5) (Hackett and Kaas, 2003, Moore et al., 1977). The pathways by which acoustic stimulation can subcortically evoke or modulate locomotor activity in mammals have not been fully elucidated (see, e.g., Felsen and Mainen, 2008) and so are not shown explicitly, but could involve connections from the superior colliculus to the locomotor regions and/or to the medullary nuclei in the descending locomotor pathway.

In summary, it can be concluded that the startle triggering hypothesis is unable to provide an account of all StartReact effects. Furthermore, there is no reason to believe that a special mechanism or pathway is needed to explain these effects, which can be more parsimoniously interpreted as being due to the operation of established mechanisms. For example, for responses that involve cortically generated commands, we argued in section 6

that StartReact effects can be understood in terms of well-established principles of motor preparation in RT tasks. The basic idea is that preparatory activation of the response circuits builds up as the expected moment of response initiation approaches and accessory stimulus-evoked activity can add to this activation. The result of this addition depends upon its size and timing: if it is sufficiently large, then it can result in the involuntary triggering of the prepared response in the absence of the imperative stimulus – a StartReact effect.

Alternatively, if it is insufficient to trigger the response, it can still shorten the RT to the IS: the effect might then be classed as intersensory facilitation as the accessory stimulus and the IS jointly contribute to response elicitation. The same logic can be applied to all instances of the StartReact effect, regardless of the pathways and brain regions involved. Sudden onset acoustic stimuli have activating or arousing effects on sensorimotor systems which might be sufficient to initiate command generation in the absence of the usual trigger signal (a StartReact effect) or they might be insufficient, in which case we observe accelerated responses (shorter RTs). This account does not exclude other types of stimuli from having similar effects on the sensorimotor system and producing StartReact-type effects (e.g., Fink et al., 2009, Hackley et al., 2009, Ruegg and Eichenberger, 1984, Marinovic et al., 2015c)

### **Conflict of Interest**

The authors have no conflict of interest to declare.

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## References

- Adams, R. A., Shipp, S. & Friston, K. J. 2013. Predictions not commands: active inference in the motor system. *Brain Structure & Function*, **218**, 611-643.
- Alibiglou, L. & MacKinnon, C. D. 2012. The early release of planned movement by acoustic startle can be delayed by transcranial magnetic stimulation over the motor cortex. *Journal of Physiology*, **590**, 919-36.
- Alstermark, B. & Isa, T. 2012. Circuits for skilled reaching and grasping. *Annual Review of Neuroscience*, **35**, 559-78.
- Ashby, F. G., Ennis, J. M. & Spiering, B. J. 2007. A neurobiological theory of automaticity in perceptual categorization. *Psychological Review*, **114**, 632-656.
- Ashby, F. G., Turner, B. O. & Horvitz, J. C. 2010. Cortical and basal ganglia contributions to habit learning and automaticity. *Trends in Cognitive Sciences*, **14**, 208-15.
- Bernstein, I. H., Clark, M. H. & Edelstein, B. A. 1969. Effects of an auditory signal on visual reaction time. *Journal of Experimental Psychology*, **80**, 567-9.
- Bjursten, L. M., Norrsell, K. & Norrsell, U. 1976. Behavioural repertory of cats without cerebral cortex from infancy. *Experimental Brain Research*, **25**, 115-30.
- Blumenthal, T. D. 1996. Inhibition of the human startle response is affected by both prepulse intensity and eliciting stimulus intensity. *Biological Psychology*, **44**, 85-104.

- Blumenthal, T. D., Reynolds, J. Z. & Spence, T. E. 2015. Support for the interruption and protection hypotheses of prepulse inhibition of startle: Evidence from a modified Attention Network Test. *Psychophysiology*, **52**, 397-406.
- Bohlin, G. & Graham, F. K. 1977. Cardiac deceleration and reflex blink facilitation. *Psychophysiology*, **14**, 423-31.
- Borra, E., Belmalih, A., Gerbella, M., Rozzi, S. & Luppino, G. 2010. Projections of the hand field of the macaque ventral premotor area F5 to the brainstem and spinal cord. *Journal of Comparative Neurology*, **518**, 2570-91.
- Borra, E., Gerbella, M., Rozzi, S., Tonelli, S. & Luppino, G. 2014. Projections to the superior colliculus from inferior parietal, ventral premotor, and ventrolateral prefrontal areas involved in controlling goal-directed hand actions in the macaque. *Cerebral Cortex*, **24**, 1054-65.
- Bowditch, H. P. & Warren, J. W. 1890. The Knee-jerk and its Physiological Modifications. *Journal of Physiology*, **11**, 25-64.
- Brooks, V. B. 1986. *The neural basis of motor control*, New York, Oxford University Press.
- Brown, P., Rothwell, J. C., Thompson, P. D., Britton, T. C., Day, B. L. & Marsden, C. D. 1991. New observations on the normal auditory startle reflex in man. *Brain*, **114** (Pt 4), 1891-902.
- Brunia, C. H. 1993. Waiting in readiness: gating in attention and motor preparation. *Psychophysiology*, **30**, 327-39.
- Bryan, W. L. & Harter, N. 1897. Studies in the physiology and psychology of the telegraphic language. *Psychological Review*, **4**, 27-53.
- Bullock, D., Cisek, P. & Grossberg, S. 1998. Cortical networks for control of voluntary arm movements under variable force conditions. *Cerebral Cortex*, **8**, 48-62.

- Bullock, D. & Grossberg, S. 1988. Neural dynamics of planned arm movements: emergent invariants and speed-accuracy properties during trajectory formation. *Psychological Review*, **95**, 49-90.
- Campbell, A. D., Squair, J. W., Chua, R., Inglis, J. T. & Carpenter, M. G. 2013. First trial and StartReact effects induced by balance perturbations to upright stance. *Journal of Neurophysiology*, **110**, 2236-45.
- Cant, N. B. & Benson, C. G. 2003. Parallel auditory pathways: projection patterns of the different neuronal populations in the dorsal and ventral cochlear nuclei. *Brain Research Bulletin*, **60**, 457-74.
- Carlsen, A. N., Chua, R., Inglis, J. T., Sanderson, D. J. & Franks, I. M. 2004a. Can prepared responses be stored subcortically? *Experimental Brain Research*, **159**, 301-9.
- Carlsen, A. N., Chua, R., Inglis, J. T., Sanderson, D. J. & Franks, I. M. 2004b. Prepared movements are elicited early by startle. *Journal of Motor Behavior*, **36**, 253-64.
- Carlsen, A. N., Chua, R., Inglis, J. T., Sanderson, D. J. & Franks, I. M. 2009. Differential effects of startle on reaction time for finger and arm movements. *Journal of Neurophysiology*, **101**, 306-14.
- Carlsen, A. N., Dakin, C. J., Chua, R. & Franks, I. M. 2007. Startle produces early response latencies that are distinct from stimulus intensity effects. *Experimental Brain Research*, **176**, 199-205.
- Carlsen, A. N. & Mackinnon, C. D. 2010. Motor preparation is modulated by the resolution of the response timing information. *Brain Research*, **1322**, 38-49.
- Carlsen, A. N., Maslovat, D., Lam, M. Y., Chua, R. & Franks, I. M. 2011. Considerations for the use of a startling acoustic stimulus in studies of motor preparation in humans. *Neuroscience and Biobehavioral Reviews*, **35**, 366-76.

- Castellote, J. M., Kumru, H., Queralt, A. & Valls-Solé, J. 2007. A startle speeds up the execution of externally guided saccades. *Experimental Brain Research*, **177**, 129-36.
- Colonus, H. & Diederich, A. 2012. Intersensory facilitation. In: SEEL, N. M. (Ed.) *Encyclopedia of the Sciences of Learning*. New York, Springer-Verlag.
- Cordo, P. J. & Nashner, L. M. 1982. Properties of Postural Adjustments Associated with Rapid Arm Movements. *Journal of Neurophysiology*, **47**, 287-382.
- Davidson, A. G., Schieber, M. H. & Buford, J. A. 2007. Bilateral spike-triggered average effects in arm and shoulder muscles from the monkey pontomedullary reticular formation. *Journal of Neuroscience*, **27**, 8053-8.
- Davis, C. M. & Beaton, R. D. 1968. Facilitation and adaptation of the human quadriceps stretch reflex produced by auditory stimulation. *Journal of Comparative and Physiological Psychology*, **66**, 483-7.
- Davis, M. 1984. The mammalian startle response. In: EATON, R. C. (Ed.) *Neural mechanisms of startle behavior*. New York, Plenum.
- Davis, M., Gendelman, D. S., Tischler, M. D. & Gendelman, P. M. 1982. A primary acoustic startle circuit: lesion and stimulation studies. *Journal of Neuroscience*, **2**, 791-805.
- Day, B. L. & Brown, P. 2001. Evidence for subcortical involvement in the visual control of human reaching. *Brain*, **124**, 1832-40.
- De Luca, C. J. 1997. The use of surface electromyography in biomechanics *Journal of Applied Biomechanics*, **13**, 135-163.
- Delval, A., Dujardin, K., Tard, C., Devanne, H., Willart, S., Bourriez, J. L., Derambure, P. & Defebvre, L. 2012. Anticipatory postural adjustments during step initiation: Elicitation by auditory stimulation of differing intensities. *Neuroscience*, **219**, 166-74.

- Desmurget, M., Epstein, C. M., Turner, R. S., Prablanc, C., Alexander, G. E. & Grafton, S. T. 1999. Role of the posterior parietal cortex in updating reaching movements to a visual target. *Nature Neuroscience*, **2**, 563-7.
- Desmurget, M. & Turner, R. S. 2010. Motor sequences and the basal ganglia: kinematics, not habits. *Journal of Neuroscience*, **30**, 7685-90.
- Diederich, A. 1995. Intersensory Facilitation of Reaction-Time - Evaluation of Counter and Diffusion Coactivation Models. *Journal of Mathematical Psychology*, **39**, 197-215.
- Diederich, A. & Colonius, H. 2004. Modeling the time course of multisensory interaction in manual and saccadic responses. In: CALVERT, G., SPENCE, C. & STEIN, B. E. (Eds.) *Handbook of Multisensory Processes*. Cambridge, MA., MIT Press.
- Doyon, J., Bellec, P., Amsel, R., Penhune, V., Monchi, O., Carrier, J., Lehericy, S. & Benali, H. 2009. Contributions of the basal ganglia and functionally related brain structures to motor learning. *Behavioural Brain Research*, **199**, 61-75.
- Drew, T., Prentice, S. & Schepens, B. 2004. Cortical and brainstem control of locomotion. *Progress in Brain Research*, **143**, 251-61.
- Erwin, R. & Buchwald, J. S. 1986. Midlatency auditory evoked responses: differential effects of sleep in the human. *Electroencephalography and Clinical Neurophysiology*, **65**, 383-92.
- Felsen, G. & Mainen, Z. F. 2008. Neural substrates of sensory-guided locomotor decisions in the rat superior colliculus. *Neuron*, **60**, 137-48.
- Fentress, J. C. 1983. The analysis of behavioral networks. In: EWERT, J. R.-P., CAPRANICA, R. R. & INGLE, D. J. (Eds.) *Advances in vertebrate neuroethology*. New York, Plenum Press.
- Fink, P. W., Kelso, J. A. & Jirsa, V. K. 2009. Perturbation-induced false starts as a test of the jirsa-kelso excitator model. *Journal of Motor Behavior*, **41**, 147-57.

- Fisher, K. M., Zaaimi, B. & Baker, S. N. 2012. Reticular formation responses to magnetic brain stimulation of primary motor cortex. *Journal of Physiology*, **590**, 4045-60.
- Fisher, R. J., Sharott, A., Kuhn, A. A. & Brown, P. 2004. Effects of combined cortical and acoustic stimuli on muscle activity. *Experimental Brain Research*, **157**, 1-9.
- Fitts, P. M. & Posner, M. 1967. *Human Performance*, Belmont CA, Brooks-Cole.
- Flynn, J. P. 1972. Patterning mechanisms, patterned reflexes, and attack behavior in cats.) *Nebraska Symposium on Motivation*.
- Foss, J. A., Ison, J. R., Torre, J. P., Jr. & Wansack, S. 1989a. The acoustic startle response and disruption of aiming: I. Effect of stimulus repetition, intensity, and intensity changes. *Human Factors*, **31**, 307-18.
- Foss, J. A., Ison, J. R., Torre, J. P., Jr. & Wansack, S. 1989b. The acoustic startle response and disruption of aiming: II. Modulation by forewarning and preliminary stimuli. *Human Factors*, **31**, 319-33.
- Fuhr, P., Cohen, L. G., Roth, B. J. & Hallett, M. 1991. Latency of motor evoked potentials to focal transcranial stimulation varies as a function of scalp positions stimulated. *Electroencephalography and Clinical Neurophysiology*, **81**, 81-9.
- Furubayashi, T., Ugawa, Y., Terao, Y., Hanajima, R., Sakai, K., Machii, K., Mochizuki, H., Shio, Y., Uesugi, H., Enomoto, H. & Kanazawa, I. 2000. The human hand motor area is transiently suppressed by an unexpected auditory stimulus. *Clinical Neurophysiology*, **111**, 178-83.
- Gielen, S. C., Schmidt, R. A. & Van den Heuvel, P. J. 1983. On the nature of intersensory facilitation of reaction time. *Perception and Psychophysics*, **34**, 161-8.
- Gironell, A., Kulisevsky, J., Roig, C., Pascual-Sedano, B., Rodriguez-Fornells, A. & Otermin, P. 2003. Diagnostic potential of acoustic startle reflex, acoustic blink reflex,



and electro-oculography in progressive supranuclear palsy: a prospective study.

*Movement Disorders*, **18**, 1273-9.

Godey, B., Schwartz, D., de Graaf, J. B., Chauvel, P. & Liegeois-Chauvel, C. 2001.

Neuromagnetic source localization of auditory evoked fields and intracerebral evoked potentials: a comparison of data in the same patients. *Clinical Neurophysiology*, **112**, 1850-9.

Gogan, P. 1970. The startle and orienting reactions in man. A study of their characteristics and habituation. *Brain Research*, **18**, 117-35.

Grillner, S. 1985. Neurobiological bases of rhythmic motor acts in vertebrates. *Science*, **228**, 143-9.

Grillner, S. 2003. The motor infrastructure: from ion channels to neuronal networks. *Nature Reviews. Neuroscience*, **4**, 573-86.

Grillner, S. 2006. Biological pattern generation: the cellular and computational logic of networks in motion. *Neuron*, **52**, 751-66.

Grillner, S., Robertson, B. & Stephenson-Jones, M. 2013. The evolutionary origin of the vertebrate basal ganglia and its role in action selection. *Journal of Physiology*, **591**, 5425-31.

Guenther, F. H. 1995. Speech sound acquisition, coarticulation, and rate effects in a neural network model of speech production. *Psychol Rev*, **102**, 594-621.

Hackett, T. A. & Kaas, J. H. 2003. Auditory pathways in the primate brain. In: GALLAGHER, M., NELSON, R. J. & WEINER, I. B. (Eds.) *Handbook of Psychology, Biological Psychology*. Hoboken, NJ, John Wiley & Sons.

Hackley, S. A., Langner, R., Rolke, B., Erb, M., Grodd, W. & Ulrich, R. 2009. Separation of phasic arousal and expectancy effects in a speeded reaction time task via fMRI. *Psychophysiology*, **46**, 163-71.

- Accepted Article
- Helminski, J. O. & Segraves, M. A. 2003. Macaque frontal eye field input to saccade-related neurons in the superior colliculus. *Journal of Neurophysiology*, **90**, 1046-62.
- Hershenson, M. 1962. Reaction time as a measure of intersensory facilitation. *Journal of Experimental Psychology*, **63**, 289-93.
- Hoffman, D. S. & Strick, P. L. 1995. Effects of a primary motor cortex lesion on step-tracking movements of the wrist. *Journal of Neurophysiology*, **73**, 891-5.
- Hoffman, H. S. & Ison, J. R. 1980. Reflex Modification in the Domain of Startle .1. Some Empirical-Findings and Their Implications for How the Nervous-System Processes Sensory Input. *Psychological Review*, **87**, 175-189.
- Honeycutt, C. F., Kharouta, M. & Perreault, E. J. 2013. Evidence for reticulospinal contributions to coordinated finger movements in humans. *Journal of Neurophysiology*, **110**, 1476-83.
- Honeycutt, C. F. & Perreault, E. J. 2012. Planning of Ballistic Movement following Stroke: Insights from the Startle Reflex. *PLoS ONE*, **7**, e43097.
- Honeycutt, C. F. & Perreault, E. J. 2014. Deficits in startle-evoked arm movements increase with impairment following stroke. *Clinical Neurophysiology*, **125**, 1682-8.
- Honeycutt, C. F., Tresch, U. A. & Perreault, E. J. 2015. Startling acoustic stimuli can evoke fast hand extension movements in stroke survivors. *Clinical Neurophysiology*, **126**, 160-4.
- Horak, F. B. & Macpherson, J. M. 1996. Postural orientation and equilibrium. In: SHEPARD, J. & ROWELL, L. (Eds.) *Handbook of Physiology*. New York, Oxford University Press.
- Ilic, T. V., Potter-Nerger, M., Holler, I., Siebner, H. R., Ilic, N. V., Deuschl, G. & Volkmann, J. 2011. Startle stimuli exert opposite effects on human cortical and spinal motor system excitability in leg muscles. *Physiological Research*, **60 Suppl 1**, S101-6.

- Ivry, R. 1996. Representational issues in motor learning: Phenomena and theory. In: HEUER, H. & KEELE, S. W. (Eds.) *Handbook of Perception and Action, Vol. 2. Motor Skills*. San Diego, CA, Academic Press.
- Iwatsubo, T., Kuzuhara, S., Kanemitsu, A., Shimada, H. & Toyokura, Y. 1990. Corticofugal projections to the motor nuclei of the brainstem and spinal cord in humans. *Neurology*, **40**, 309-12.
- Jean, A. 2001. Brain stem control of swallowing: neuronal network and cellular mechanisms. *Physiological Reviews*, **81**, 929-69.
- Jordan, L. M., Liu, J., Hedlund, P. B., Akay, T. & Pearson, K. G. 2008. Descending command systems for the initiation of locomotion in mammals. *Brain Research Reviews*, **57**, 183-91.
- Kawai, R., Markman, T., Poddar, R., Ko, R., Fantana, A. L., Dhawale, A. K., Kampff, A. R. & Olveczky, B. P. 2015. Motor cortex is required for learning but not for executing a motor skill. *Neuron*, **86**, 800-12.
- Keele, S. W. 1968. Movement control in skilled motor performance. *Psychological Bulletin*, **70**, 387-403.
- Keele, S. W., Cohen, A. & Ivry, R. 1990. Motor programs: Concepts and issues. In: JEANNEROD, M. (Ed.) *Attention and performance XIII*. Hillsdale, NJ, Erlbaum.
- Kelly, R. M. & Strick, P. L. 2004. Macro-architecture of basal ganglia loops with the cerebral cortex: use of rabies virus to reveal multisynaptic circuits. *Brain Mechanisms for the Integration of Posture and Movement*, **143**, 449-459.
- Kiehn, O. 2006. Locomotor circuits in the mammalian spinal cord. *Annual Review of Neuroscience*, **29**, 279-306.

- Koch, M., Lingenhohl, K. & Pilz, P. K. 1992. Loss of the acoustic startle response following neurotoxic lesions of the caudal pontine reticular formation: possible role of giant neurons. *Neuroscience*, **49**, 617-25.
- Kuhn, A. A., Sharott, A., Trottenberg, T., Kupsch, A. & Brown, P. 2004. Motor cortex inhibition induced by acoustic stimulation. *Experimental Brain Research*, **158**, 120-4.
- Kumru, H., Urra, X., Compta, Y., Castellote, J. M., Turbau, J. & Valls-Solé, J. 2006. Excitability of subcortical motor circuits in Go/noGo and forced choice reaction time tasks. *Neuroscience Letters*, **406**, 66-70.
- Kumru, H. & Valls-Solé, J. 2006. Excitability of the pathways mediating the startle reaction before execution of a voluntary movement. *Experimental Brain Research*, **169**, 427-32.
- Kuriki, S., Nogai, T. & Hirata, Y. 1995. Cortical sources of middle latency responses of auditory evoked magnetic field. *Hearing Research*, **92**, 47-51.
- Kuypers, H. G. J. M. 1958. Corticobulbar Connexions to the Pons and Lower Brain-Stem in Man - an Anatomical Study. *Brain*, **81**, 364-&.
- Landis, C. & Hunt, W. A. 1939. *The Startle Pattern*, New York, Farrar & Rinehart.
- Lang, C. E. & Schieber, M. H. 2004. Reduced muscle selectivity during individuated finger movements in humans after damage to the motor cortex or corticospinal tract. *Journal of Neurophysiology*, **91**, 1722-33.
- Latash, M. L. & Anson, J. G. 1996. What are “normal movements” in atypical populations? *Behavioral and Brain Sciences* **19**, 55-68.
- Leichnetz, G. R., Spencer, R. F., Hardy, S. G. P. & Astruc, J. 1981. The Prefrontal Corticotectal Projection in the Monkey - an Anterograde and Retrograde Horseradish-Peroxidase Study. *Neuroscience*, **6**, 1023-1041.

- Lemon, R. N. 2008. Descending pathways in motor control. *Annual Review of Neuroscience*, **31**, 195-218.
- Leuthold, H., Sommer, W. & Ulrich, R. 2004. Preparing for action: Inferences from CNV and LRP. *Journal of Psychophysiology*, **18**, 77-88.
- Liang, M., Mouraux, A. & Iannetti, G. D. 2013. Bypassing primary sensory cortices--a direct thalamocortical pathway for transmitting salient sensory information. *Cerebral Cortex*, **23**, 1-11.
- Liegeois-Chauvel, C., Morin, C., Musolino, A., Bancaud, J. & Chauvel, P. 1989. Evidence for a contribution of the auditory cortex to audiospinal facilitation in man. *Brain*, **112** ( Pt 2), 375-91.
- Lingenhohl, K. & Friauf, E. 1992. Giant neurons in the caudal pontine reticular formation receive short latency acoustic input: an intracellular recording and HRP-study in the rat. *Journal of Comparative Neurology*, **325**, 473-92.
- Lingenhohl, K. & Friauf, E. 1994. Giant neurons in the rat reticular formation: a sensorimotor interface in the elementary acoustic startle circuit? *Journal of Neuroscience*, **14**, 1176-94.
- Linzenbold, W. & Himmelbach, M. 2012. Signals from the deep: reach-related activity in the human superior colliculus. *Journal of Neuroscience*, **32**, 13881-8.
- Lipp, O. V., Kaplan, D. M. & Purkis, H. M. 2006. Reaction time facilitation by acoustic task-irrelevant stimuli is not related to startle. *Neuroscience Letters*, **409**, 124-7.
- Los, S. A. & van den Heuvel, C. E. 2001. Intentional and unintentional contributions to nonspecific preparation during reaction time foreperiods. *Journal of Experimental Psychology: Human Perception and Performance*, **27**, 370-86.
- Luce, R. D. 1986. *Response times: Their role in inferring elementary mental organization*, New York, Oxford University Press.

- MacKinnon, C. D., Allen, D. P., Shiratori, T. & Rogers, M. W. 2013. Early and unintentional release of planned motor actions during motor cortical preparation. *PLoS ONE*, **8**, e63417.
- MacKinnon, C. D., Bissig, D., Chiusano, J., Miller, E., Rudnick, L., Jager, C., Zhang, Y. H., Mille, M. L. & Rogers, M. W. 2007. Preparation of anticipatory postural adjustments prior to stepping. *Journal of Neurophysiology*, **97**, 4368-4379.
- Margolis, R. H. & Levine, S. C. 1991. Acoustic reflex measures in audiologic evaluation. *Otolaryngologic Clinics of North America*, **24**, 329-47.
- Marinovic, W., Cheung, F. L., Riek, S. & Tresilian, J. R. 2014a. The effect of attention on the release of anticipatory timing actions. *Behavioral Neuroscience*, **128**, 548-55.
- Marinovic, W., de Rugy, A., Lipp, O. V. & Tresilian, J. R. 2013. Responses to loud auditory stimuli indicate that movement-related activation builds-up in anticipation of action. *Journal of Neurophysiology*, **109**, 996-1008.
- Marinovic, W., de Rugy, A., Lipp, O. V. & Tresilian, J. R. 2015a. Reply to Maslovat et al. *Journal of Neurophysiology*, **113**, 3455-3456.
- Marinovic, W., de Rugy, A., Riek, S. & Tresilian, J. R. 2014b. The early release of actions by loud sounds in muscles with distinct connectivity. *Experimental Brain Research*, **232**, 3797-802.
- Marinovic, W., Flannery, V. & Riek, S. 2015b. The effects of preparation and acoustic stimulation on contralateral and ipsilateral corticospinal excitability. *Human Movement Science*, **42**, 81-88.
- Marinovic, W., Milford, M., Carroll, T. & Riek, S. 2015c. The facilitation of motor actions by acoustic and electric stimulation. *Psychophysiology*.

- Marinovic, W., Tresilian, J. R., de Rugy, A., Sidhu, S. & Riek, S. 2014c. Corticospinal modulation induced by sounds depends on action preparedness. *Journal of Physiology*, **592**, 153-69.
- Martin, J. H. 2005. The corticospinal system: from development to motor control. *Neuroscientist*, **11**, 161-73.
- Maschke, M., Drepper, J., Kindsvater, K., Kolb, F. P., Diener, H. C. & Timmann, D. 2000. Involvement of the human medial cerebellum in long-term habituation of the acoustic startle response. *Experimental Brain Research*, **133**, 359-67.
- Maslovat, D., Franks, I. M., Leguerrier, A. & Carlsen, A. N. 2015. Responses to startling acoustic stimuli indicate that movement-related activation is constant prior to action: a replication with an alternate interpretation. *Physiological Reports*, **3**.
- Maslovat, D., Kennedy, P. M., Forgaard, C. J., Chua, R. & Franks, I. M. 2012. The effects of prepulse inhibition timing on the startle reflex and reaction time. *Neuroscience Letters*, **513**, 243-7.
- Mcclean, M. D. & Sapir, S. 1983. Audio-Motor Reflexes in Lower Lip Motor Units Having Different Recruitment Thresholds. *Brain Research*, **264**, 293-296.
- McDowell, J. E., Dyckman, K. A., Austin, B. P. & Clementz, B. A. 2008. Neurophysiology and neuroanatomy of reflexive and volitional saccades: evidence from studies of humans. *Brain and Cognition*, **68**, 255-70.
- McLoon, L. K. 1998. Muscle fiber type compartmentalization and expression of an immature myosin isoform in the sternocleidomastoid muscle of rabbits and primates. *Journal of Neurological Sciences*, **156**, 3-11.
- Meincke, U., Mörth, D., Voss, T. & Gouzoulis-Mayfrank, E. 2002. Electromyographical differentiation between the acoustic blink and startle reflex. Implications for studies

- investigating startle behavior. *European Archives of Psychiatry and Clinical Neuroscience*, **252**, 141-145.
- Miller, J. 1982. Divided attention: evidence for coactivation with redundant signals. *Cognitive Psychology*, **14**, 247-79.
- Milner, A. D. & Goodale, M. A. 2006. *The Visual Brain in Action*, Oxford, Oxford University Press.
- Miyachi, S., Hikosaka, O. & Lu, X. 2002. Differential activation of monkey striatal neurons in the early and late stages of procedural learning. *Experimental Brain Research*, **146**, 122-6.
- Moller, A. R. 2003. *Sensory systems anatomy and physiology*, San Diego, Calif., Academic Press.
- Moore, J. K., Karapas, F. & Moore, R. Y. 1977. Projections of the inferior colliculus in insectivores and primates. *Brain, Behavior and Evolution*, **14**, 301-27.
- Moors, A. & De Houwer, J. 2006. Automaticity: a theoretical and conceptual analysis. *Psychol Bull*, **132**, 297-326.
- Murofushi, T., Matsuzaki, M. & Wu, C. H. 1999. Short tone burst-evoked myogenic potentials on the sternocleidomastoid muscle: are these potentials also of vestibular origin? *JAMA Otolaryngology - Head & Neck Surgery*, **125**, 660-4.
- Nickerson, R. S. 1973. Intersensory facilitation of reaction time: energy summation or preparation enhancement? *Psychological Review*, **80**, 489-509.
- Nonnekes, J., Carpenter, M. G., Inglis, J. T., Duysens, J. & Weerdesteyn, V. 2015. What startles tell us about control of posture and gait. *Neuroscience and Biobehavioral Reviews*, **53**, 131-138.



- Nonnekes, J., Geurts, A. C., Nijhuis, L. B., van Geel, K., Snijders, A. H., Bloem, B. R. & Weerdesteyn, V. 2014a. Reduced StartReact effect and freezing of gait in Parkinson's disease: two of a kind? *Journal of Neurology*, **261**, 943-50.
- Nonnekes, J., Oude Nijhuis, L. B., de Niet, M., de Bot, S. T., Pasman, J. W., van de Warrenburg, B. P., Bloem, B. R., Weerdesteyn, V. & Geurts, A. C. 2014b. StartReact restores reaction time in HSP: evidence for subcortical release of a motor program. *Journal of Neuroscience*, **34**, 275-81.
- Nonnekes, J., Scotti, A., Oude Nijhuis, L. B., Smulders, K., Queralt, A., Geurts, A. C., Bloem, B. R. & Weerdesteyn, V. 2013. Are postural responses to backward and forward perturbations processed by different neural circuits? *Neuroscience*, **245**, 109-20.
- Packard, M. G. & Knowlton, B. J. 2002. Learning and memory functions of the Basal Ganglia. *Annu Rev Neurosci*, **25**, 563-93.
- Paltsev, Y. I. & Elnor, A. M. 1967. Change in the functional state of the segmental apparatus of the spinal cord under the influence of sound stimuli and its role in voluntary movement. *Biophysics*, **12**, 1219-1226.
- Pfaff, D. W. 1999. *Drive: Neural and Molecular Mechanisms for Sexual Motivation*, Cambridge, MA, The MIT Press.
- Philipp, R. & Hoffmann, K. P. 2014. Arm Movements Induced by Electrical Microstimulation in the Superior Colliculus of the Macaque Monkey. *Journal of Neuroscience*, **34**, 3350-3363.
- Pieron, H. 1914. Recherches sur les lois de variation des temps de latence sensorielle en fonction des intensités excitatrices. *L'Année Psychologique* **20**, 17-96.
- Porter, R. & Lemon, R. 1995. *Corticospinal function and voluntary movement*, Oxford, Clarendon Press.

- Accepted Article
- Queralt, A., Valls-Solé, J. & Castellote, J. M. 2008. The effects of a startle on the sit-to-stand manoeuvre. *Experimental Brain Research*, **185**, 603-9.
- Raab, D. H. 1962. Statistical facilitation of simple reaction times. *Transactions of the New York Academy of Sciences*, **24**, 574-90.
- Raptis, H., Burtet, L., Forget, R. & Feldman, A. G. 2010. Control of wrist position and muscle relaxation by shifting spatial frames of reference for motoneuronal recruitment: possible involvement of corticospinal pathways. *Journal of Physiology*, **588**, 1551-70.
- Requin, J., Brener, J. & Ring, C. 1991. Preparation for action. In: JENNINGS, J. R. & COLES, M. G. H. (Eds.) *Handbook of cognitive psychophysiology: Central and autonomic nervous system approaches*. New York, Wiley.
- Reynolds, R. F. & Day, B. L. 2007. Fast visuomotor processing made faster by sound. *Journal of Physiology*, **583**, 1107-15.
- Robinson, D. A. 1975. Oculomotor control signals. In: LENNERSTRAND, G. & BACH-Y-RITA, P. (Eds.) *Basic Mechanisms of Ocular Motility and their Clinical Implications* Oxford, pergamon.
- Rogers, M. W., Kennedy, R., Palmer, S., Pawar, M., Reising, M., Martinez, K. M., Simuni, T., Zhang, Y. H. & MacKinnon, C. D. 2011. Postural preparation prior to stepping in patients with Parkinson's disease. *Journal of Neurophysiology*, **106**, 915-924.
- Rosenbaum, D. A. 2009. *Human Motor Control*, New York, Academic Press.
- Rosengren, S. M., Welgampola, M. S. & Colebatch, J. G. 2010. Vestibular evoked myogenic potentials: past, present and future. *Clinical Neurophysiology*, **121**, 636-51.
- Rossignol, S. 1975. Startle responses recorded in the leg of man. *Electroencephalography and clinical neurophysiology*, **39**, 389-97.

- Rossignol, S. & Jones, G. M. 1976. Audio-spinal influence in man studied by the H-reflex and its possible role on rhythmic movements synchronized to sound. *Electroencephalography and Clinical Neurophysiology*, **41**, 83-92.
- Rothwell, J. C. 2006. The startle reflex, voluntary movement, and the reticulospinal tract. *Supplement in Clinical Neurophysiology*, **58**, 223-31.
- Ruegg, D. G. & Eichenberger, A. 1984. Effects of electrical stimulation of low-threshold muscle afferents on visual reaction time. *Electroencephalography and Clinical Neurophysiology*, **57**, 184-7.
- Rushworth, G. 1962. Observations on blink reflexes. *Journal of Neurology, Neurosurgery, and Psychiatry*, **25**, 93-108.
- Samuels, E. R. & Szabadi, E. 2008. Functional neuroanatomy of the noradrenergic locus coeruleus: its roles in the regulation of arousal and autonomic function part I: principles of functional organisation. *Current Neuropharmacology*, **6**, 235-53.
- Sapir, S., McClean, M. D. & Larson, C. R. 1983. Human laryngeal responses to auditory stimulation. *Journal of the Acoustical Society of America*, **73**, 315-21.
- Schall, J. D. 2002. The neural selection and control of saccades by the frontal eye field. *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences*, **357**, 1073-82.
- Schmidt, R. A. 1982. *Motor Control and Learning: A Behavioral Emphasis* Champaign Illinois, Human Kinetics.
- Schmidt, R. A. & Lee, T. D. 2011. *Motor Control and Learning: A Behavioral Emphasis*, Champaign Illinois, Human Kinetics.
- Schouenborg, J. 2008. Action-based sensory encoding in spinal sensorimotor circuits. *Brain Research Reviews*, **57**, 111-7.

- Scott, S. H. 2008. Inconvenient truths about neural processing in primary motor cortex. *Journal of Physiology*, **586**, 1217-24.
- Scudder, C. A., Kaneko, C. S. & Fuchs, A. F. 2002. The brainstem burst generator for saccadic eye movements: a modern synthesis. *Experimental Brain Research*, **142**, 439-62.
- Shadmehr, R. & Wise, S. P. 2005. *The Computational Neurobiology of Reaching and Pointing*, Cambridge MA, MIT Press.
- Siegmund, G. P., Inglis, J. T. & Sanderson, D. J. 2001. Startle response of human neck muscles sculpted by readiness to perform ballistic head movements. *Journal of Physiology*, **535**, 289-300.
- Simons, R. C. 1996. *Boo! Culture, Experience and the Startle Reflex*, Oxford, Oxford University Press.
- Simonyan, K. 2014. The laryngeal motor cortex: its organization and connectivity. *Current Opinion in Neurobiology*, **28**, 15-21.
- Simonyan, K. & Horwitz, B. 2011. Laryngeal motor cortex and control of speech in humans. *Neuroscientist*, **17**, 197-208.
- Snoddy, G. S. 1926. Learning and stability: A psychophysical analysis of a case of motor learning with clinical applications. *Journal of Applied Psychology*, **10**, 1-36.
- Sokolov, E. N. 1963. Higher nervous functions; the orienting reflex. *Annual Review of Physiology*, **25**, 545-80.
- Sparks, D. L. 2002. The brainstem control of saccadic eye movements. *Nature Reviews Neuroscience*, **3**, 952-64.
- Stevenson, A. J., Chiu, C., Maslovat, D., Chua, R., Gick, B., Blouin, J. S. & Franks, I. M. 2014. Cortical involvement in the StartReact effect. *Neuroscience*, **269C**, 21-34.

- Summers, J. J. & Anson, J. G. 2009. Current status of the motor program: revisited. *Human Movement Science*, **28**, 566-77.
- Takakusaki, K. 2008. Forebrain control of locomotor behaviors. *Brain Research Reviews*, **57**, 192-8.
- Thackray, R. I. & Touchstone, R. M. 1970. Recovery of motor performance following startle. *Perceptual and Motor Skills*, **30**, 279-92.
- Todd, J. W. 1912. *Reaction to multiple stimuli*, New York., The Science Press.
- Todd, N. 2001. Evidence for a behavioral significance of saccular acoustic sensitivity in humans. *Journal of the Acoustical Society of America*, **110**, 380-90.
- Tonolli, I., Aurenty, R., Lee, R. G., Viallet, F. & Massion, J. 2000. Lateral leg raising in patients with Parkinson's disease: influence of equilibrium constraint. *Movement Disorders*, **15**, 850-61.
- Tourville, J. A. & Guenther, F. H. 2011. The DIVA model: A neural theory of speech acquisition and production. *Language and Cognitive Processes*, **26**, 952-981.
- Tresilian, J. R. 2012. *Sensorimotor Control and Learning: An Introduction to the Behavioral Neuroscience of Action*, Palgrave Macmillan.
- Tresilian, J. R. & Plooy, A. M. 2006. Effects of acoustic startle stimuli on interceptive action. *Neuroscience*, **142**, 579-94.
- Turvey, M. T. 2009. Nature of motor control: Not strictly "motor", not quite "control". In: STERNAD, D. (Ed.) *Progress in motor control: A multidisciplinary perspective*. New York, Springer Verlag.
- Uchino, Y., Sato, H., Sasaki, M., Imagawa, M., Ikegami, H., Isu, N. & Graf, W. 1997. Sacculocollic reflex arcs in cats. *Journal of Neurophysiology*, **77**, 3003-12.
- Valls-Solé, J. 2012. Assessment of excitability in brainstem circuits mediating the blink reflex and the startle reaction. *Clinical Neurophysiology*, **123**, 13-20.

- Valls-Solé, J., Kofler, M., Kumru, H., Castellote, J. M. & Sanegre, M. T. 2005. Startle-induced reaction time shortening is not modified by prepulse inhibition. *Experimental Brain Research*, **165**, 541-8.
- Valls-Solé, J., Kumru, H. & Kofler, M. 2008. Interaction between startle and voluntary reactions in humans. *Experimental Brain Research*, **187**, 497-507.
- Valls-Solé, J., Rothwell, J. C., Goulart, F., Cossu, G. & Munoz, E. 1999. Patterned ballistic movements triggered by a startle in healthy humans. *Journal of Physiology*, **516 ( Pt 3)**, 931-8.
- Valls-Solé, J., Sole, A., Valdeoriola, F., Munoz, E., Gonzalez, L. E. & Tolosa, E. S. 1995. Reaction time and acoustic startle in normal human subjects. *Neuroscience Letters*, **195**, 97-100.
- Vlasak, M. 1969. Effect of startle stimuli on performance. *Aerospace Medicine*, **40**, 124-8.
- Welch, R. B. & Warren, D. H. 1986. Intersensory interactions. In: BOFF, K. R., KAUFMAN, L. & THOMAS, J. P. (Eds.) *Handbook of perception and human performance*. New York, Wiley.
- Werner, W., Dannenberg, S. & Hoffmann, K. P. 1997. Arm-movement-related neurons in the primate superior colliculus and underlying reticular formation: comparison of neuronal activity with EMGs of muscles of the shoulder, arm and trunk during reaching. *Experimental Brain Research*, **115**, 191-205.
- Wolpaw, J. R. 2007. Spinal cord plasticity in acquisition and maintenance of motor skills. *Acta Physiologica*, **189**, 155-69.
- Woodhead, M. M. 1958. The effects of bursts of loud noise on a continuous visual task. *British Journal of Industrial Medicine*, **15**, 120-5.
- Woodworth, R. S. 1938. *Experimental Psychology*, New York, Holt.

- Accepted Article
- Wu, C. H., Young, Y. H. & Murofushi, T. 1999. Tone burst-evoked myogenic potentials in human neck flexor and extensor. *Acta Otolaryngologica*, **119**, 741-4.
- Wu, T., Chan, P. & Hallett, M. 2008. Modifications of the interactions in the motor networks when a movement becomes automatic. *Journal of Physiology*, **586**, 4295-304.
- Yin, H. H. & Knowlton, B. J. 2006. The role of the basal ganglia in habit formation. *Nature Reviews. Neuroscience*, **7**, 464-76.
- Ziemann, U., Tergau, F., Netz, J. & Homburg, V. 1997. Delay in simple reaction time after focal transcranial magnetic stimulation of the human brain occurs at the final motor output stage. *Brain Research*, **744**, 32-40.

### Captions

**Figure 1:** Mean ( $\pm$ SD) premotor reaction time from stimulus onset as a function of intensity in dBa and the presence of startle response indicators. Black circles are means for trials in which neither Orbicularis Oris (OOc) nor sternocleidomastoid (SCM) were recorded. Blue triangles are means for trials in which OOc was observed but not SCM. Red squares are means for trials in which SCM observed. \* Significant difference from nri. \*\* Significant difference from nri and OOc only. Reproduced from Carlsen et al. (2007).

**Figure 2:** Premotor reaction time distribution in 10 ms bins, separated by those trials with SCM activation (SCM+, black bars) and without SCM activation (SCM-, white bars), for probe time at -40 ms before the imperative stimulus. Reproduced from Maslovat et al. (2015), Figure 4B.

**Figure 3:** Hypothetical cortical circuits underlying the triggering of responses by loud auditory stimuli. **A.** Transmission to motor cortical areas via the auditory cortex. **B** – Transmission to motor cortical areas directly from the thalamus. Adapted from Marinovic, Tresilian, et al., (2014c).

**Figure 4:** Histograms of RT distributions for loud stimulus (115 dB) trials in the distal task (finger abduction response, top) and the proximal task (20° elbow extension response, bottom) from Carlsen et al.'s (2009) study. Data from both SCM+ trials and SCM- trials are shown. RTs were placed in 10 millisecond bins and the number in each bin is shown as a percentage of the total number of loud stimulus trials for each task. Data from Carlsen et al. (2009), Figure 4.

**Figure 5:** Schematic diagram showing the major descending projections from the cortex to subcortical motor regions and structures, between subcortical structures and from the brain into the spinal cord. Individual cortical loci are not shown and no significance attaches to the locations at which the arrows representing descending pathways originate. The cerebellum, lateral connections and ascending pathways are omitted for clarity, but the basal ganglia-thalamocortical loop is included. Also shown are the major routes by which activity evoked by acoustic stimulation reaches various parts of the brain. KEY: SOC = superior olivary complex, IC = inferior colliculus, EOM nuclei = extra-ocular muscle nuclei, DLR/STLR/MLR = diencephalic/subthalamic/mesencephalic locomotor regions, SNc/SNr = substantia nigra pars compacta/pars reticulata, GPi/GPe = Globus pallidus interna/externa, STN = subthalamic nucleus, CPG = central pattern generator. Solid arrow heads = (primarily) excitatory connections, filled circles = inhibitory connections.



Figures

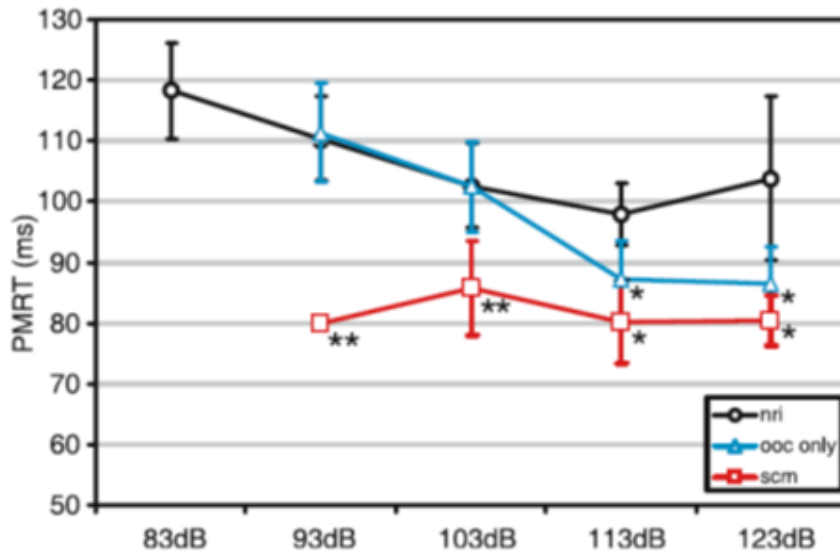


Figure 1

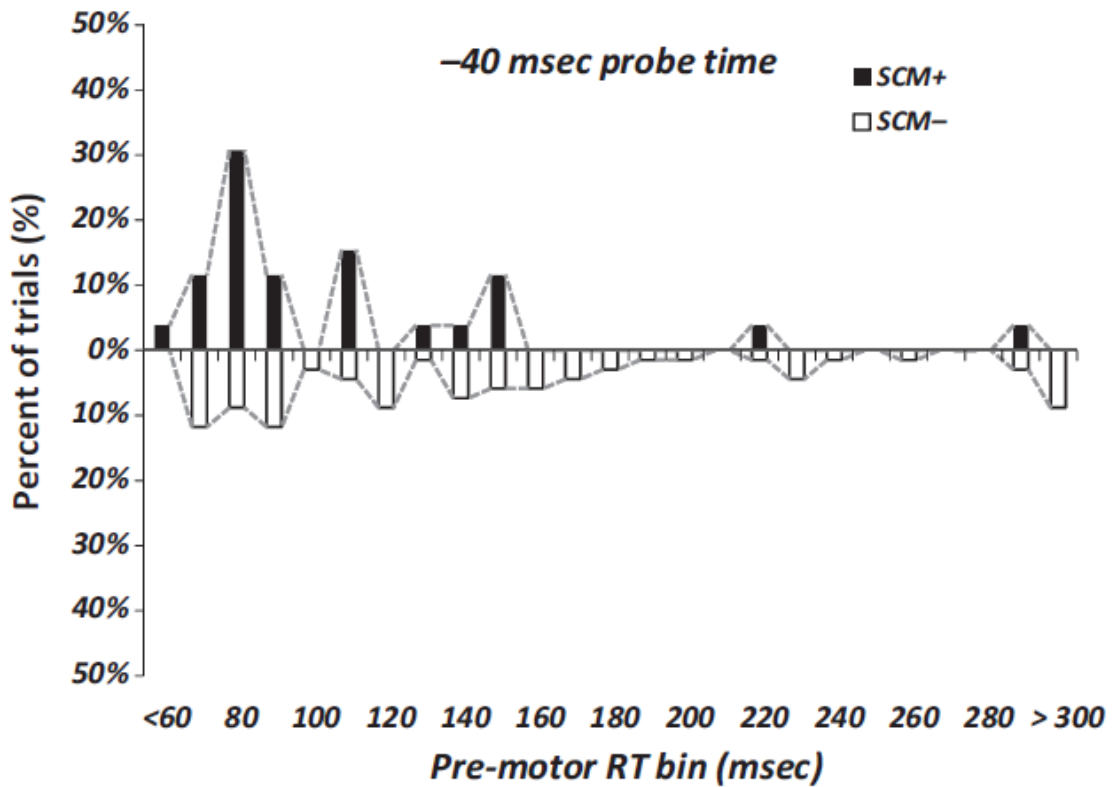


Figure 2

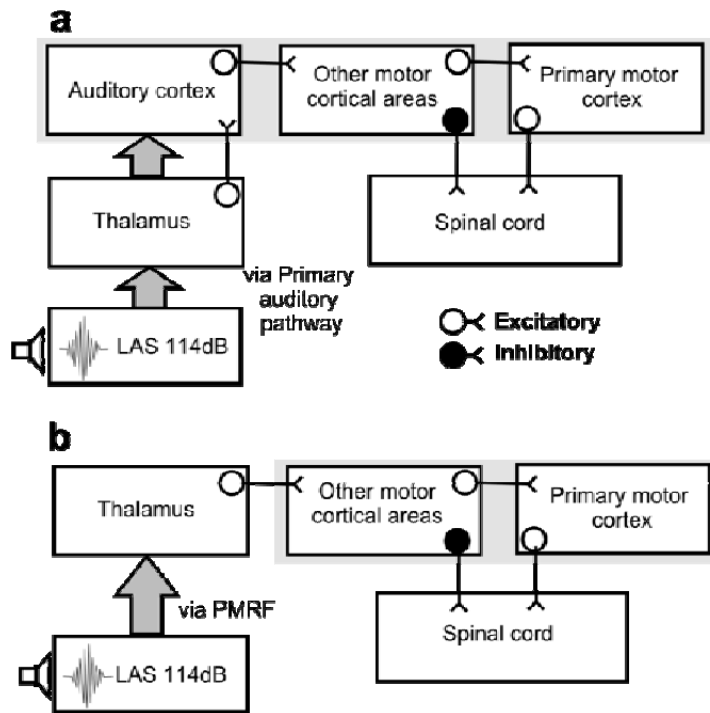


Figure 3

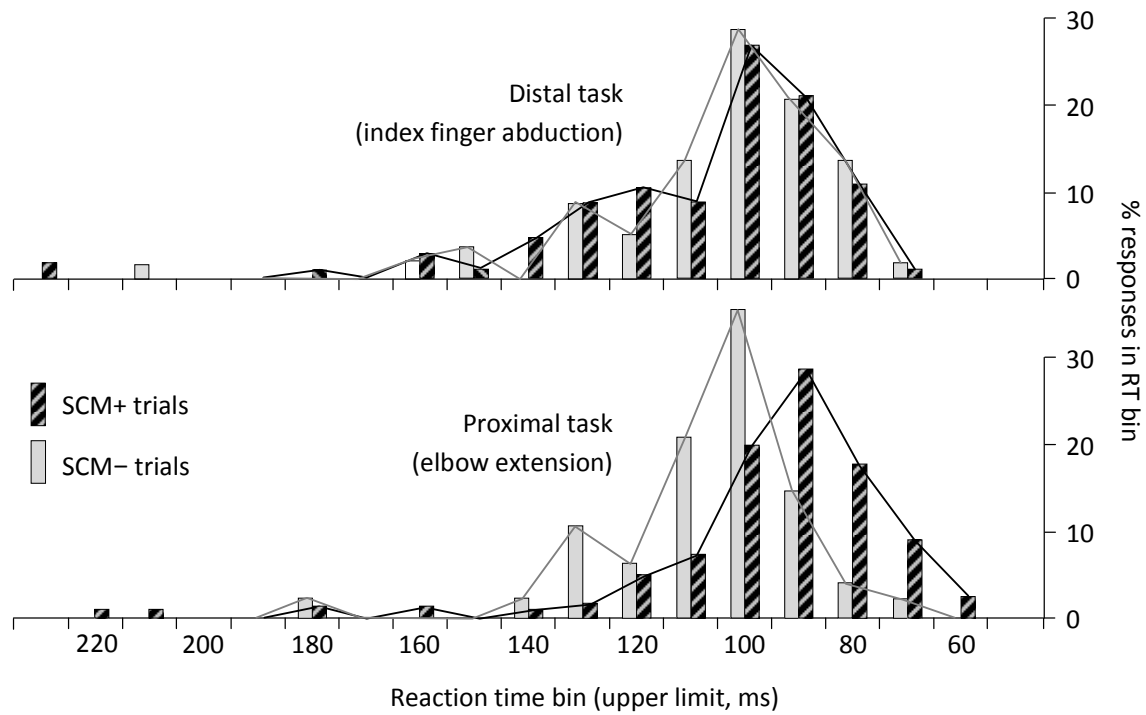


Figure 4

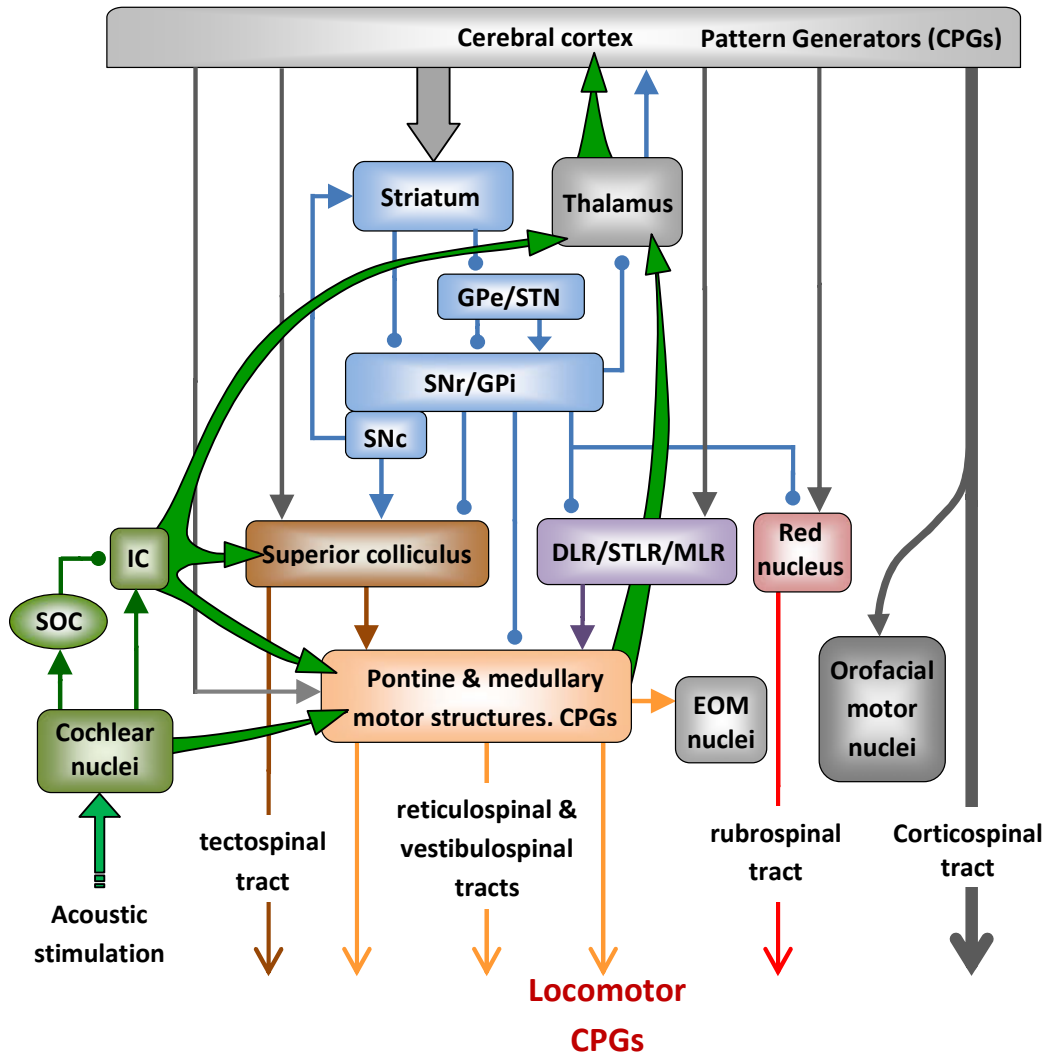


Figure 5