



Cognitive and personality analysis of startle reactivity in a large cohort of healthy males



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ABSTRACT

Subjects with low/undetectable startle are usually excluded from startle studies but few reports not confounded by this factor, show reduced startle in healthy impulsive subjects, or clinical populations with disorders of affect and impulsivity but also in schizophrenia and its prodrome. We examined the relationship of startle reactivity including startle “non-responding” status to cognitive and affective personality traits in a large and ethnically/demographically homogeneous cohort of healthy males from the LOGOS study, Heraklion, Crete. Startle reactivity was monotonically related to sensitivity to reward (higher in “non-responders”, lower in strong responders). In addition, “non-responders” had poorer strategy, working memory and sustained attention performance compared to responder tertile groups. More research in clinical and high risk populations is required to examine if low/undetectable startle reactivity is a valuable intermediate phenotype for disorders of affect and impulsivity. It is possible that the “non-responsive” status may capture disease related features such as executive dysfunction.

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1. Introduction

The startle reflex is a ubiquitous, cross-species reflexive response to abrupt and intense stimulation. It consists of a rapid striated muscle contraction designed to facilitate the flight reaction and/or to move the organism away of an unexpected threat. The reflex is subserved by a well defined neural circuitry whereby afferents from the cochlea, trigeminal nucleus, and vestibular nuclei reach the caudal pontine reticular nucleus (PnC, the center of the reflex), which then projects to motor areas of cranial nerve nuclei and the spinal cord (Koch & Schnitzler, 1997). As the vestibular and trigeminal nuclei are also activated by vestibular and tactile stimuli, respectively, and the vestibulospinal tract converges with the reticulospinal tract in the spinal cord, a cross-modal processing of startle stimuli occurs at this level (Li, Steidl, & Yeomans, 2001). The startle

reflex is straightforward to elicit, record and quantify in the animal and human laboratory using similar stimuli and techniques. The most common technique is startle elicitation following short and abrupt acoustic stimuli of high intensity (acoustic startle reflex – ASR), although visual or cutaneous stimuli have also been used successfully to elicit startle. In all modalities, the startle response is modulated by the duration, the intensity and the rise time of the stimuli. Although electromyographic recording of the activity of the orbicularis oculi muscle is the most employed technique for assessing the startle response, other effective procedures have also been suggested (e.g. electrophysiologic recording of the eyelid and direct recording of eyelid movement; for review, see Berg & Balaban, 1999).

The ASR shows interesting forms of regulation, which are of great relevance to psychiatric research. For instance, the ASR to a sudden intense stimulus (pulse) can be inhibited by a preceding weak sensory stimulus (the prepulse), which is presented 30–500 ms before the startling stimulus (Graham, 1975), a phenomenon known as prepulse inhibition (PPI). PPI is observed with both discrete and continuous prepulses, it increases with higher prepulse duration and intensity and the optimal prepulse-pulse interval is around 100 ms for both humans and animals (for review see Blumenthal, 1999). PPI is thought to reflect “sensorimotor gating”, a form of central nervous system inhibition wherein distracting sensory information is filtered out during the early stages

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of processing (Braff et al., 1978). Deficient PPI is a surrogate measure of psychosis in animal models and a candidate endophenotype for schizophrenia (Calkins et al., 2007) with significant applications in schizophrenia research (Roussos, Giakoumaki, Adamaki, & Bitsios, 2011a; Roussos, Giakoumaki, & Bitsios, 2009a; Roussos, Giakoumaki, Adamaki, Georgakopoulos, et al., 2011; Roussos et al., 2006). Prepulse facilitation (PPF) refers to the enhancement of startle magnitude when the inter-stimulus interval is either very short (<30 ms) or relatively long (>500 ms) (Graham, 1975). PPF at long inter-stimulus intervals is thought to reflect an orienting response to incoming information (Graham, 1980) and has been found deficient in schizophrenia patients (Ludewig, Geyer, & Vollenweider, 2003) and their unaffected siblings (Wynn et al., 2004). Also, the potentiation of startle magnitude by conditioned or contextual threat, has become a translational psychophysiological paradigm, particularly useful in the study of normal and pathological fear and anxiety in experimental animals, healthy human subjects and patients with psychiatric syndromes (Grillon & Baas, 2003). Finally, startle enhancement or attenuation when the reflex is elicited in the presence of affectively unpleasant or pleasant experimental conditions (usually pictorial stimuli) has been termed “affective startle modulation” (Lang, Bradley, & Cuthbert, 1990) and has become a prominent methodological tool in the study of human emotion and its disorders. This pattern of startle modulation has been observed regardless of the modality of the startle probe but the degree of modulation depends on laterality, the duration of the affective stimulus and the time point of startle stimulus delivery after picture onset (for review, see Bradley, Cuthbert, & Lang, 1999).

While the ASR regulation from early attentional processes and internal affective/motivational states has been exploited in fruitful translational psychiatric research over the last twenty years, relatively little research efforts have been allocated to startle reactivity or ‘baseline’ startle in the absence of any experimental manipulation. While startle magnitude shows very large between-subject variability, it is highly heritable (Anokhin, Heath, Myers, Ralano, & Wood, 2003; Hasenkamp et al., 2010) with considerable consistency within subjects across time (Larson, Ruffalo, Nietert, & Davidson, 2000). It is possible that individual differences in baseline startle reactivity may reflect activity of its regulatory brain structures (e.g. limbic) due to constitutional factors. Subjects with low/undetectable startle are usually excluded from startle studies but few reports not confounded by this factor (see Quednow et al., 2006 for a discussion of this point), showed reduced startle reactivity in healthy, high sensation seeking Asians (Swerdlow, Talledo, & Braff, 2005), and high novelty seeking Caucasian males (Roussos, Giakoumaki, & Bitsios, 2009). Interestingly, the low startle healthy Caucasian males in the study of Roussos, Giakoumaki, and Bitsios (2009) were carrying the long DRD4 variable number tandem repeat (L-DRD4 VNTR) polymorphism, which is implicated in sensitivity to reward and disorders with dysregulated affect and impulsivity (Roussos, Giakoumaki, & Bitsios, 2009). Consistent with the above, one study found reduced or entirely absent startle reactivity in psychopaths (Herpertz, Werth, Lukas, et al., 2001), while our group found reduced startle reactivity in remitted bipolar disorder (BD) patients and their unaffected siblings (Giakoumaki et al., 2010). One way of better understanding such constitutional factors underlying reduced startle reactivity in patient populations, is to examine cognitive and affective correlates of startle reactivity in healthy subjects devoid of the confounds of medication, presence of symptoms and the brain effects of chronic psychiatric illness. Learning about cognitive and emotional correlates of startle reactivity may advance our understanding of both startle reactivity and the disorders characterized by reduced startle. We therefore used our LOGOS cohort of healthy young males in Heraklion, Crete (Roussos, Giakoumaki, Adamaki, & Bitsios, 2011) to explore potential differences in personality traits and cognitive profile between

subgroups with high, intermediate, low and blunt/undetectable acoustic startle reactivity. Based on the literature cited above, we hypothesized initially, that low reactivity subgroups would present with the highest levels of sensitivity to reward. Given that startle reactivity deficits may emerge with the onset of acute psychosis (Quednow et al., 2008) and reduced startle has also been found in schizophrenia patients (Quednow et al., 2006), we also hypothesized that low reactivity subgroups would present with reduced performance in measures of executive function.

Subjects with blunt/undetectable startle have been frequently characterized in the literature as “non-responders”, as opposed to “responders” i.e. the rest of the population who present with some startle response. Informal reports estimate, somehow vaguely, that about 5–10% of the general population (and a higher percentage from clinical populations) are “startle non-responders”, i.e. they exhibit startle responses on too few trials or none at all (Blumenthal et al., 2005), in the absence of any perceptual (i.e. auditory) impairments. However, studies vary substantially in the criteria used for the identification of startle “non-responders” (Table 1 in Supplementary data). These subjects are excluded from startle studies and it is hard to know whether they represent the low end of a continuum (weak responses which are lost in the EMG noise floor) or a qualitatively distinct population (genuine non-responding status). With the above considerations in mind, we used a fairly standard session (see Section 2 and Supplementary data) and equipment (San Diego, SR-LAB) similar to most research groups in the field, ensuring that recording environment, equipment setup, participant preparation, and data handling were all of sufficient sensitivity according to published guidelines (Berg & Balaban, 1999; Blumenthal et al., 2005) to allow for any possible very small responses to be detected. As in some previous studies (e.g. Csomor et al., 2009; Kumari et al., 2008), we set the criterion for response at 10 μ V, the smallest detectable startle amplitude on our equipment. Subjects with zero response probability in the 12 pulse-alone trials were positively defined as “non-responders”. Subjects with too few (1–3 out of 12) and sporadic responses which did not allow for calculation of a reliable startle were also defined as “non-responders” (see Section 2). Moreover, in order to confirm maximum sensitivity of the recording, we compared the EMG activity in the first 20 ms of recording between responders and “non-responders”, to exclude the possibility that lack of startle in “non-responders” could be due to excessive noise occluding small responses. Finally, in additional analyses, we treated the “non responders” as a qualitatively separate group distinct from all other subjects clustered together as “responders”, to ensure that potential differences in personality and cognition would not reflect peculiarities associated with the strong responders rather than the non-responders.

2. Methods

2.1. Participants

Participants were recruited from the first wave of the LOGOS (Learning On Genetics Of Schizophrenia Spectrum) study in Heraklion, Crete. The LOGOS project recruited 1149 randomly selected Greek Caucasian young male conscripts from the Greek Army (mean age 22.32 ± 3.78 ; range: 18–29), during its first phase between June 2008 and August 2010. The study took place between 9 am and 3 pm in the medical quarters of the Military Training Camp of Candidate, Supply Army Officers (S.E.A.P) in Heraklion, Crete. For this purpose, two adjacent rooms in the medical quarters were converted into laboratories. Following public presentation of the study’s methods and goals in each consecutive series of new conscripts, all participants willing to volunteer, had a detailed information sheet and gave written informed consent before screening. All participants were tested on one single occasion at some point during their two months military training in this establishment.

All participants had been recently screened for current physical and mental health status by the army medical authorities and were physically healthy and free from any DSM Axis I disorders. However, they all underwent a review of their medical history, the Mini-International Neuropsychiatric Interview (M.I.N.I.) interview (Sheehan et al., 1998), urine toxicology and IQ testing with the Raven’s Progressive

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