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Scientific evaluation committee CES37 Neurosciences Intégratives et Cognitives			

Sensory and Emotional Processing In Autism spectrum disorders - SEPIA

Summary table of persons involved in the project

Partner	Name	First Name	Current position	Role & responsibilities in the project (4 lines max)	Involvement (person.month) throughout the project's total duration
UMR1253 iBrain INSERM - Tours	**GOMOT**	**Marie**	**CRCN**	**Coordinator, Partner's 1 scientific leader, Involved in WPs 1, 2, 3**	**30 p.month**
UMR1253 iBrain INSERM	Wardak	Claire	CRCN	Member, expertise in psychophysiological recordings, protocol setting and data analysis supervision	4 p.month
UMR1253 iBrain INSERM	Bonnet-Brilhault	Frédérique	PU-PH	Member, diagnostic and recruitment of patients with ASD	6 p.month
UMR1253 iBrain INSERM	Aguillon-Hernandez	Nadia	MCU	Member, psychophysiological recordings in ASD, protocol setting and data analysis supervision	4 p.month
UMR1253 iBrain INSERM	*To be recruited*		*PhD*	*PhD student in charge of WPs 1- 2- 3 experiments in ASDs and aged-matched controls*	*36 p.month*
UMR1253 iBrain INSERM	*To be recruited*		*Trained clinician*	*clinical assessment of participants with ASD*	*6 p.month*
UMR9912 IRCAM- Paris	**AUCOUTURIER**	**Jean-Julien**	**CRCN CNRS**	**Partner's 2 scientific leader Involved in WP 1, 3**	**15 p.month**
UMR9912 IRCAM	SUSINI	Patrick	DR IRCAM	Member, expertise in psychoacoustics and temporal integration	9 p.month
UMR9912 IRCAM	MISDARIIS	Nicolas	CR IRCAM	Member, expertise in sound design and reverse-correlation	7.2 p.month
UMR9912 IRCAM	*To be recruited*		*Post doctoral position*	*Post doc in charge of WP2-3 experiments and analyses in typically developed participants*	*20 p.month*

Any changes that have been made in the full proposal compared to the pre-proposal: No change.

I. Proposal's context, positioning and objectives

a. Objectives and research hypothesis

With approximately 67 million individuals affected worldwide and a prevalence of 1/150, Autism Spectrum Disorder (ASD) is the fastest growing neurodevelopmental disorder (Lyall et al., 2017). In France, this condition affects approximately 600,000 individuals, who have a major handicap in daily life adaptation. Autism, with four successive national health programs specifically dedicated to the syndrome, is now recognized as a national public health priority. Yet so far, no biological or biochemical markers exist to improve diagnosis or therapy for ASD. Identifying the core socio-emotional and/or

cognitive deficits operating in ASD, thereby better understanding the physiopathology of the disorder, is key to improve this situation.

ASDs covers a wide variety of clinical profiles which share two main dimensions, appearing from childhood: a marked impairment in social communication on the one hand, and repetitive behaviour, restricted interests coupled with sensory peculiarities on the other hand (APA, 2013). Although this dyad of symptoms is required for clinical diagnosis, current research in ASD so far has basically been dissociated into two subfields (socio-emotional; cognitive/sensory), and very few studies have attempted to integrate these two aspects. Yet, both unusual responses to sensory input and abnormal social functioning could be linked to impairment in the processing of auditory and visual stimuli, and especially when these stimuli have socio-emotional content as is the case for voices or faces (Bonnet-Brilhault et al., 2018). **Whether difficulties in ASD are related to emotion-specific deficits, to sensory particularities which would be even more manifest for socio-emotional stimuli, or to both, therefore remains to be established**.

The co-occurrence of atypical sensory processing and unusual/absent emotional reactions in ASD is notably well documented in the context of vocal emotional prosody, one of the first social stimuli to which the developing child is exposed. Atypical prosodic production is a hallmark of ASD and has been linked to social awkwardness (Grossman, 2015) and poor children socialization skills (Paul et al., 2005). In parallel, adults and children with ASD also have lower performance on emotional prosody perception than controls (Peppe et al., 2007). That atypical behaviors in both the perception and production of vocal emotions should co-occur in ASD suggests a general impairment of the emotional perception-action loop, which mechanisms are believed to be essential to emotional contagion, convergence and theory-of-mind (Prochazkova and Kret, 2017).

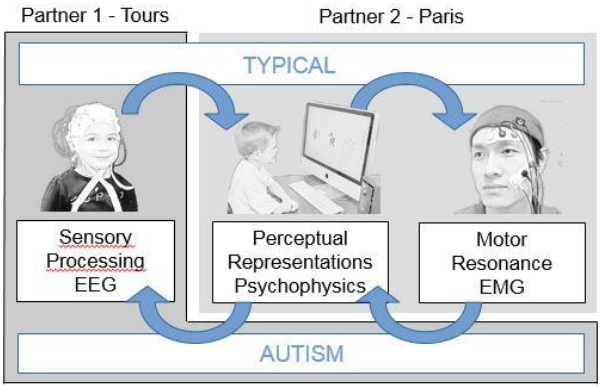

Fig. 1: Project SEPIA, the collaboration of an INSERM Autism team in Tours and a CNRS sound-technology laboratory in Paris, combines the methodologies of electrophysiology, psychophysics and audio signal processing to explore, all three major levels of the emotional perception-representation-action chain in autistic participants.

Project SEPIA aims, for the first time, to explore all three major steps of the emotional perception-action chain in the same participants (Sensory processing at the neurophysiological level – Perceptual representation at the psychophysical level – Motor resonance at the behavioral level, see Fig. 1)**, using the highly-emblematic case-study of the smiling voice as an experimental model**. Smiling, the bilateral contraction of the zygomatic muscles, is one of the most iconic behavior in the human emotional repertoire, and the lack of social smile is one of the most recurrent early signs of ASD (Dawson et al., 1990). During both adult-directed speech and motherese, smiling has specific acoustic consequences which change the phonological signature of vowels by stretching vocal formants (Piazza et al., 2017; Ponsot et al., 2018a) Like visual smiles, smiled voice triggers automatic and unconscious facial imitations (Arias et al., 2018). Thus, by exploring how neutral and smiling voices are processed down the perception-action chain in patients and controls, from stimulus sensory encoding to emotional perception and auditory-facial mimicry, **project SEPIA will allow to disentangle the influence of sensory/perceptive and emotion-related processes and provide novel mechanistic insights into the socio-emotional difficulties of children and adults with ASD**.

Results expected from the project are two-fold. First, by using elegant experimental paradigms (roving sequences, reverse correlation and auditory-facial mimicry) that proved in the recent past to provide very useful information in typical adults, and which will be modified for the purpose of the project, new insights will be generated on the **pathophysiological processes at play in ASD at each separate step of the perception-action loop:** whether and how the encoding of stimulus regularity (WP1), psychoacoustic processing of smiled speech (WP2) and explicit and implicit mechanisms of mimicry (WP3), differ between ASD participants and controls. Second, by conducting all steps in the same participants in a tight consortium of two highly-complementary partners, the project will provide a rare opportunity to **generate knowledge about the multi-stage interactions of atypical processing**.

b. Position of the project as it relates to the state of the art

Sensory processing

A lot of our consortium's previous work (**Partner 1 - Tours**) has focused on change processing in ASD. With electroencephalography (EEG) investigations and clinical assessment, we identified a link between atypical brain responses to auditory deviancy, and behavioral difficulties related to resistance to change (Gomot et al, 2011). We, and others, further showed that atypical change-detection in ASD was even more marked in response to emotional deviants in vocal prosody, these auditory sounds being among the most modulated and unpredictable in daily life (Charpentier et al., 2018; Lindström et al., 2016). However, while automatic change-detection in ASD has received broad research interest, **the way patients encode the converse phenomenon of sensory regularities, and whether that encoding is differently affected for socio-emotional stimuli, remains largely unexplored.** Yet, adaptation to the sensory environment is essential to quickly detect and respond to changes, anticipate future events, and ultimately to communicate and to notice emotions in others. Contextual regularities, i.e. the sensory memory traces to which e.g. deviants are normally compared in oddball paradigms, allow observers to extract regular patterns and to develop stable perceptual representations. In addition, their atypical encoding could be a possible basis for Bayesian theories (Friston 2005) which propose to explain the full ASD symptomatology by an imbalance in the contribution of priors relatively to sensory inputs (Pellicano and Burr 2012; Palmer et al., 2017). The Bayesian brain requires the learning of sensory regularities in order to build up predictions from past sensations and these prediction processes may thus be critical to adaptive cognitive and social functions: for instance, recent studies have suggested that ASD is characterized by a disinclination to infer generalization rules based on the extraction of regularities (Sapey-Triomphe et al., 2018).

The neurophysiological process underlying the encoding of sensory regularity, the Repetition-Suppression (RS) (Haenschel et al., 2005), translates at the cerebral level as a decrease in the neuronal response to increasing repetitions of a stimulus (Schacter et al., 2004; Grill-Spector et al., 2006). In a preliminary study in typical adults, EEG allowed us to identify the time course of this neuronal adaptation in response to repeated vocal or non-vocal stimuli. **Our pilot data showed that the temporal dynamics of regularity encoding differed according to the nature of the stimuli,** with richer vocal stimuli requiring further processing than non-vocal sounds before leading to a full neural adaptation (Gomot et al., in prep). In ASD, research with children have provided strong evidence for reduced behavioral and neural adaptation in the visual domain (Nordt et al., 2016), with a possible improvement throughout development. An fMRI study compared regularity encoding of social and non-social stimuli in ASD and showed reduced RS to faces but typical RS to shapes, suggesting a specific alteration in social stimuli neural adaptation (Ewbank et al., 2017). In the auditory domain, the rare studies of regularity encoding in ASD have reported an absence of Repetition suppression (Martineau et al., 1992; Kolesnik et al., 2019) but, while adaptation to vocal sounds regularity is essential to extract relevant information for social communication, these were only conducted with pure tones

repetitions. To our knowledge, the brain correlates of the encoding of repetitive emotional vocal stimulation have never been studied in ASD, nor across development.

The 'sensory' part of the project (WP1, below) therefore intends to apply this original EEG paradigm to ASD participants, furthering our understanding of the brain processes involved in the development of stable perceptual representations. We will study regularity encoding and change detection in ASD, and how these depend on the emotional nature of the information.

Perceptual representations

Both the recognition and production of emotions rely on internal representations of the underlying physical characteristics of each expression. In the visual modality, atypical mental representations of facial expressions in ASD have been described either by asking participants to imitate the expressions (Brewer et al., 2016) or using psychophysical reverse correlation methods, which are able to reverse-engineer participants' mental representations in stimulus space by analyzing their responses to large sets of systematically-varied stimuli (Ewing et al., 2018; Vilidaite, et al., 2017). However, **almost nothing is known about how people with ASD internally represent vocal expressions of emotions.** In a reverse-correlation perspective, cognitive deficits in recognizing emotional voice stimuli can result from atypical internal representations (e.g. misrepresenting the typical spectral shape of a vocal smile, see Fig. 2), and/or inconsistent processing of the sensory input by these internal models (which the technique models as an additive source of "internal noise" on the decision variable, see Murray 2011). Both aspects (shape and internal noise) can be measured experimentally, and are known to be impacted by individual differences. For instance in Varnet et al. (2016), the internal time-frequency representations that dyslexic participants used for phoneme discrimination had a different shape than controls; in Burred et al. (2019), it was the amount of internal noise involved in the discrimination of sung melodies which correlated negatively with the amount of musical training of the participants. Project SEPIA will be first to apply the auditory reverse-correlation methodology to ASD, clarifying how it affects the shape of mental representations, and the amount of internal noise with which these representations process sensory input, and thus providing important mechanistic insights into how ASD participants process emotional vocal signals.

In a recent work (**Partner 2 - Paris**), **we created a novel paradigm combining reverse correlation and digital voice-transformation algorithms** to uncover how typical adults internally represented the spectral signature of smiled-voice (Ponsot et al., 2018b). Our preliminary data shows that these representations were remarkably robust within individuals, processed with a low level of internal noise (comparable to lower-level vision tasks, Neri 2010) and predictive of behavior: the 'smile' signature applied to new sounds was also identified as smiling, and these sounds triggered unconscious facial reactions in listeners, who automatically smiled when they listened to them (Arias et al. 2018).

The 'representation' part of the project will adapt the paradigm of reverse-correlation to children and adults with ASD in order to fully characterize the auditory representations of smiled voice in autism, and test their impact on both sensory (above) and motor (below) processes.

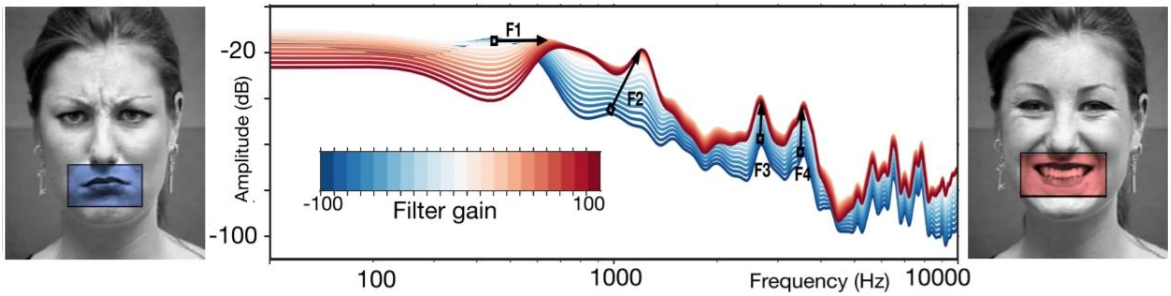

Fig.2: Average mental representation (over N=10 typical adults) of the spectral changes that makes a single phoneme [a] sound smiling (red) or non-smiling (blue). Participants evaluate sounds as more smiling when their spectral envelope is warped to increase the frequency of formant F1, the frequency and amplitude of F2, and the amplitudes of F3 and F4. Figure adapted from Ponsot, Arias & Aucouturier (2018).

Motor resonance

Spontaneous mimicry, notably that of facial expressions like smiling, is a crucial socio-emotional skill for empathy and communication. These skills are often impacted in ASD (McIntosh et al., 2006), but task-differences in the literature (e.g., whether participants are explicitly instructed to attend to the emotional characteristics of the stimuli or not) have made it difficult to conclude on the mechanisms that underlie differences with controls. In Oberman et al. (2009), facial reactions of ASD participants were found slower than controls when mimicry was spontaneous, but not when they were imitating voluntarily, which suggests that ASD participants may engage in compensatory strategies. However, Press et al. (2010) found that, in an interference task, participants ASD did not differ from controls in automatic imitation of emotional facial gestures. Other studies in ASD have address another component of empathy, affective resonance, the weakness of which might directly lead to an inability to decode and be sensitive to others' emotional states. Studies in children with ASD have reported a lack of contagious yawning, considered as an index of 'emotional contagion' (Helt et al., 2010). If still debatable in the visual modality (with a suppression of the between-group effect when attention toward the facial stimuli is controlled, see Usui et al., 2013), the effect seems especially robust for auditory yawning (Giganti and Esposito Ziello, 2009). So far, it therefore **remains unclear whether impairments in facial mimicry result from abnormal sensory or attentional processing which hinders the perception of the action triggering emotion, from a general impairment in imitation (Hamilton, 2013), or from a mere absence of emotional contagion.**

Emotional contagion also involves an automatic adjustment of the autonomic nervous system (Porges and Furman 2011) resulting in modulations of the activity of several ANS effectors like the iris muscles, that control pupil diameter according to the emotional arousal (Bradley et al. 2008). Pupil dilation has also been documented in response to emotional sound stimuli (Babiker et al., 2015) and would constitute an implicit measure of emotional contagion resulting in autonomous modulation.

In our recent work, **we have used smiled speech to design an electromyography (EMG) paradigm enabling to separate explicit and implicit mimicry responses** (e.g. measuring zygomatic reactions even when smiles are not consciously recognized). Our data showed that typical adult listeners display spontaneous zygomatic muscles contraction to smiled voice, and that part of these reactions are independent from participants' explicit judgments of stimulus smiliness (Arias et al., 2018).

The 'motor resonance' part of the project will adapt this 'facial mimicry' paradigm to children and adults with ASD, using stimuli tuned to the typical and atypical auditory representations of smiled voice uncovered in part 'perceptual representation' of the project. By separating explicit and implicit EMG responses in the same participants, and possibly autonomic reactions, we will avoid confounding compensatory strategies which, notably for patients with high-cognitive level, has plagued previous research.

c. Methodology and risk management

Our work plan makes full use of the **complementary expertise and previous work of the 2 project partners** which, collectively, span all three stages of the smiled-voice perception-action chain, and both typical and ASD adults and children research (Fig.1). Our research program involves three main work packages to achieve our objectives.

WP1. To explore brain processes involved in the establishment of auditory regularity in a context of emotional vocal stimuli, we will perform EEG recordings while participants are presented with a roving paradigm which entails trains of repeated smiling or neutral voices. Event-related potentials (ERPs) will be studied using combined analysis of scalp potentials and scalp current densities maps, and electrical source estimation in order to specify the brain regions involved and to show the dynamics of their activation.

WP2. To characterize the representation of auditory smile in typical and ASD participants, we will conduct reverse-correlation experiments in which participants evaluate the smiliness of a large number of spoken stimuli with randomized spectral properties. Mental representations will be computed from participant responses using the classification image procedure, and internal noise levels will be estimated with double-pass consistency measures.

WP3. To assess the motor and autonomic mimicry, behavioural (ratings), facial electromyography (EMG) and pupillometry data will be collected while participants are instructed to listen to vocal expressions and to judge the smiliness of the stimuli. Signal detection theory analyses will allow separating explicit and implicit responses, i.e. muscle activity that correlates with detected stimuli (hits and correct rejections) or with undetected stimuli (misses and false alarms).

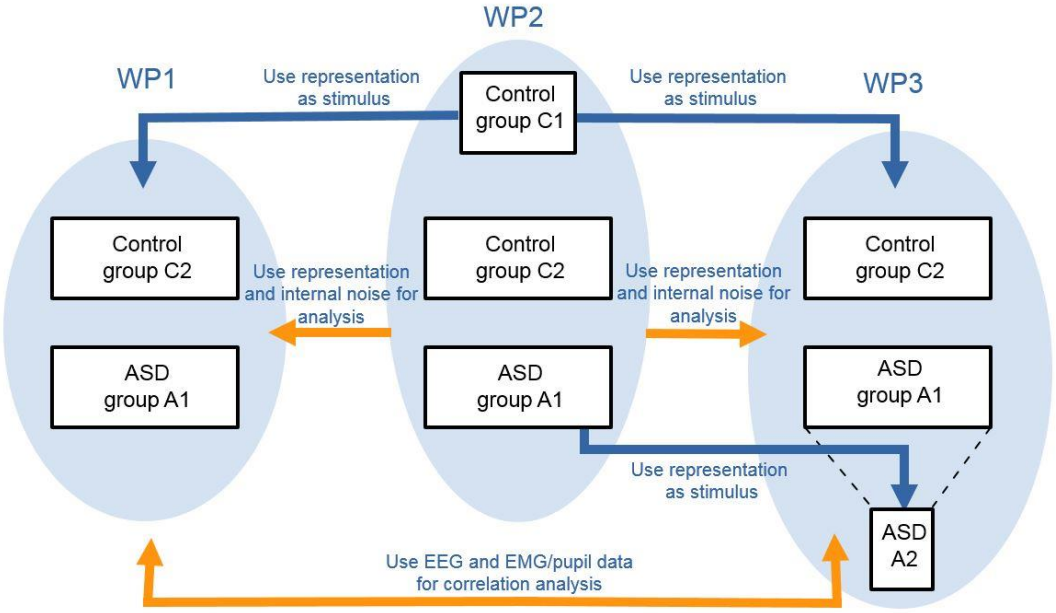

Fig. 3: Schematic description of the relationships between WPs aiming at collecting and opposing measures at all three stages of processing to study their interaction, i.e. stimuli derived from the reverse correlation experiments of WP2 will be used in the EEG experiments of WP1 and the EMG and pupil experiments of WP3.

Experiments in each these WPs document each stage of the perception-action chain, are innovative per se, and can be analyzed independently. However, one additional originality of the project is to assess all three steps in the same participants, and study their respective contributions in ASD sensory and socio-emotional processing. To this aim, experiments in WP1 and WP3 will use information derived from the reverse-correlation experiments of WP2 (Fig. 3), following this organization: The EEG,

behavioral and EMG/pupillometry studies of WP1-2-3 will be carried out in children and adults. Population will include 25 children aged 7-12yrs and 25 adults with ASD (A1), and 50 aged and gender matched typical controls (C2). The study of the representation of vocal smile (WP2) will also involve a larger typical population (C1) of 40 children aged 7-12 years (20 subjects by age range of 3 years) and 20 adults, whose recruiting will begin earlier to provide age-related 'normative' mental representations which will be used to create the stimuli delivered in WP1 and WP3.
Then EEG, pupillometry and EMG data obtained in WP1 and WP3 will be regressed on the distance between the participant's own mental representation and that of the control group, as well as on the participant's amount of internal noise. Finally, a selection of high-functioning ASD participants (A2) will also take part in an additional WP3 experiment that directly compare EMG responses and pupillometry to individualized stimuli from WP2, with those to less-specific control-group representations.

WP1 - Sensory processing of vocal emotion

This WP focusses on sensory regularities encoding, a process which allows for the development of stable perceptual representations. By comparing brain responses to a new stimulus and to the same stimulus after it's been repeated many times, it is possible to separate the electrophysiological index of auditory regularity encoding, called the Repetition Positivity (RP), which increases with the number of repetitions (Haenschel et al., 2005; Costa-Faidella et al., 2011), and varies according to the characteristics of the repeated information.

Objectives

- Characterize EEG brain activity associated with regularity encoding and automatic change detection, using neutral and smiling vowel sounds, as well as unfamiliar vowel sounds, in a passive 'roving' paradigms (Partner 1). Compare RP responses to these vocal stimuli between ASD participants and controls, and across development (Partner 1).
- Study the impact of individual mental representations and internal noise, derived from WP2, on RP responses (Partner 2).

Stimulus sequence and Procedure

We will used a roving paradigm (Cowan et al., 1993, Baldeweg et al., 2004) in which trains of stimulation of different vocal quality are presented, each composed of the same stimulus called standard which is repeated n times (depending on the length of the train). The first stimulus of each train is considered as deviant compared to the preceding repeated standard, and then becomes standard due to repetition. We will use trains of 4, 8 and 14 repetitions of the same stimulus, delivered in a pseudo-random order (Fig.4). The sequence will comprise 5 different vocal stimuli that will be adapted to compare between neural responses to smiled vowels (e.g. smiled [a] and smiled [e]), and to neutral vowels (e.g. neutral [a] and [e]), and an 'unfamiliar hybrid' stimulus between [a] and [e]. Smiled stimuli for the roving paradigm will be created using the mental representations derived from the reverse correlation experiments conducted in WP2 on C1 (partner 2). Hence we will be able to compare the establishment of regularity encoding for emotional, neutral, and unfamiliar information. Each stimulus will be delivered for 300ms via two speakers. 120 repetitions of each train length will be presented, resulting in a recording time of approximately half an hour. During EEG recording, subjects will watch a silent movie without subtitles while sounds are delivered, with the instruction that they'll have to briefly describe the movie's plot at the end of the session.

Population

Twenty-five children aged 7-12yrs, 25 adults with ASD, and 50 age- and gender- matched typical controls will take part to WP1. Patients will be recruited and clinically characterised as described in section 'Clinical population' below. Clinical assessment and brain investigations will be performed in the iBrain INSERM unit, by a multidisciplinary staff.

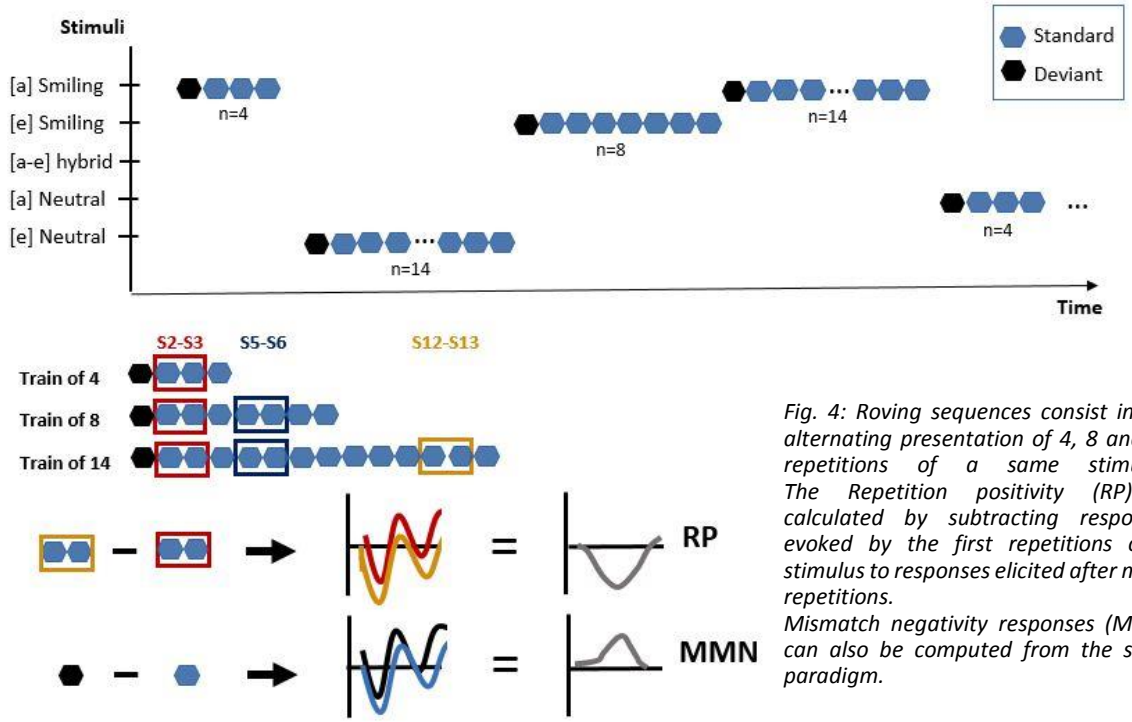

Fig. 4: Roving sequences consist in the alternating presentation of 4, 8 and 14 repetitions of a same stimulus. The Repetition positivity (RP) is calculated by subtracting responses evoked by the first repetitions of a stimulus to responses elicited after many repetitions.
Mismatch negativity responses (MMN) can also be computed from the same paradigm.

Data acquisition and analysis

Subjects will be presented with the sound sequences, while their electroencephalogram (EEG) will be recorded through the ActiveTwo BioSemi® electrode system from 64 scalp electrodes referenced to the nose. EEG epochs will be averaged separately for the different standard positions in the trains, and for the deviant stimuli. ERPs will be studied using combined analysis of scalp potentials and scalp current densities maps and electrical source estimation in order to specify the brain regions involved and to show the dynamics of their activation. Amplitudes and latencies will be analysed using repeated measure analysis of variance (ANOVA) with Group (controls, ASD) as between-subjects factor, and Electrode X Position in the train (beginning/final) X Stimulus type (Smiling/neutral/unfamiliar) as within-subjects factors. Sources location will be calculated using the Curry® software, based on sLORETA multiple discrete sources estimation.
The stimuli used in the EEG sequences, derived in WP2 from the mental representation of a control group, will necessarily vary in sensory distance from the mental representation of each subject. The distance between the mental representation of each participant and the group norm, as well as each participant's level of internal noise, will be used to inform EEG analyzes, using regressions or ANCOVAs.

Predictions

- Participants with ASD might display atypical RP responses to sounds repetitions.
- **Smiling effect:** Smiling voices possibly require further processing than neutral vowels before leading to a full neural adaptation. This specific encoding of vocal emotional stimuli repetition might be particularly impaired for participants with ASD.

- Non-familiarity effect: The regularity of prototypical smiling stimuli should be encoded more rapidly than non-familiar stimuli in controls. Such difference might not be observed in ASD, suggesting that patients display no clear prototypical representation.
- Developmental effect: In controls, stronger representations in adults should lead to sharper RPs than in children for prototypical smiling voice. Differences between ASD and controls may be more marked for children than adults, because of increased expertise and compensatory strategies (Charpentier et al., 2018).

WP2 – Perceptual representation of vocal emotion

This WP focusses on the auditory representations from which individuals are able to recognize emotional speech, and in particular the spectral signature of speech pronounced with a smile. Recent experimental paradigms based on reverse correlation (Ponsot et al. 2018b) are able to measure the shape of these representations, as well as the amount of internal noise reflecting the consistency of the filtering of sensory input by these representations.

Objectives

- Adapt previous work on emotional reverse-correlation in Ponsot et al. (2018b) to control (partner 2) and ASD (partner 1) children and adults, by simplifying and reducing the number of responses needed.
- Provide a full characterization of the auditory representations of smiled voice in ASD, both qualitatively and quantitatively (how robust are representations with respect to internal noise, (Vilidaite et al., 2017) (partner 1).
- Study the impact of these representations by selecting personalized stimuli to further inform analysis in experiments of WP1 and 3 (partner 2).

Stimulus and procedure

Stimuli will consist of recordings of phonemes (ex. [a]), pronounced with constant pitch by a single speaker with a neutral expression. We will then produce many spectral variants of these baseline stimuli by manipulating their spectral characteristics using a random frequency equalizer composed of 25 linearly interpolated, log-separated frequency points spaced between 100 and 10 000Hz, with gain values drawn from Gaussian distributions [standard deviation (SD) +/- 5 dB clipped at +/- 2.5 SD].

For adult controls, the experiments will consist of a single session per phoneme including 6 blocks of 100 trials. Using a 2-alternative forced choice procedure, participants will be presented pairs of randomly- filtered voices and asked in each pair which of the two appeared to have been produced with the greatest smile. Trials presented in the first 5 blocks will be all different, but the 100 trials of the sixth block will be the same as those presented in the fifth block. This double-pass procedure is used to evaluate the percentage of agreement and thus the level of internal noise for each observer in the task (Neri, 2010).

For children and ASD participants, the procedure will be adapted and will use a reduced number of trials, to achieve an experiment duration of less than 12 minutes.

Population

An initial group of control participants (C1, Fig.3), N=20 adults and N=40 children (7-12 years-old) will be used to compute generic mental representations of smiled phonemes, which will serve as stimuli for the EEG and EMG/pupillometry experiments of WP1 and WP3. Then, the reverse-correlation procedure will be repeated on the same population as WP1 and WP3 (see above), in order to characterize individual representations and internal noise levels.

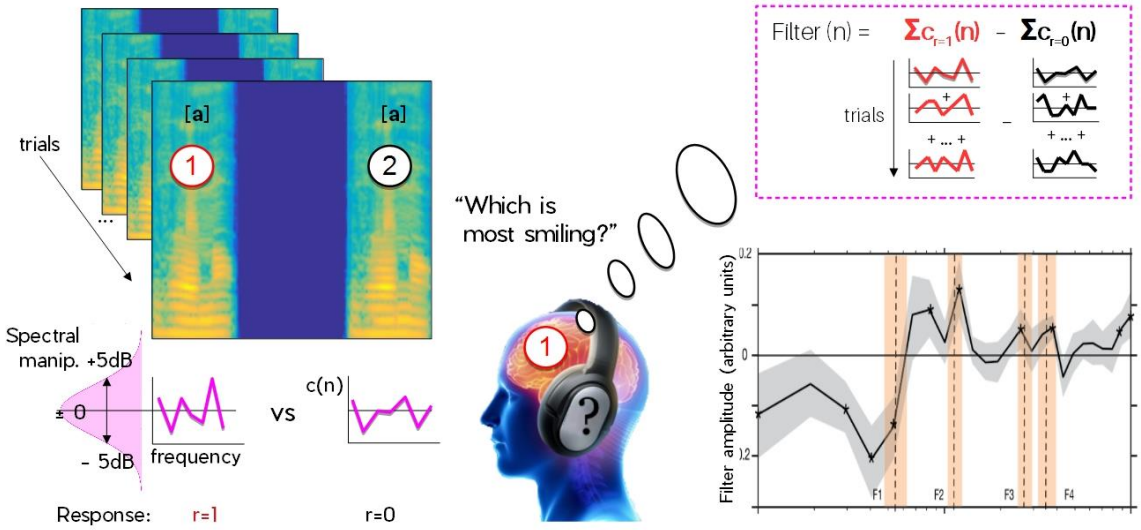

Fig. 5: Schematic representation of the reverse correlation procedure. (Left) Utterances of the single recording of phoneme [a] are digitally manipulated to have random spectral content c(n). Participants are presented with several hundred pairs of manipulated phonemes and judged which is most smiling. (Right) Mental representations (or filters) are computed as the mean spectral shape of the voices perceived as smiling, minus those judged non-smiling. The resulting mental representation, computed here on judgements of N=10 typical adults, corresponds to a spectral filter which displaces energy before and after the first formant (F1), and increases energy on the position of F2,F3 and F4. Applied to a new sound, this filter has the effect illustrated in Fig. 2.

Data analysis

Individual frequency filter (a 25-points vector) will be computed for each subject as the mean filter of the voices classified as smiling from which we subtract the mean filter of the remaining voices that were not chosen as smiling by the participant (Fig.5). Internal noise levels for each participant will be computed using a signal detection theory model with late additive noise, fitted to participant's consistency over the last two experimental blocks (Neri, 2010).

Predictions

- ASD participants may differ from controls on the shape of their mental representations (e.g. less precise tuning to phoneme formant).
- ASD participants may also differ from controls with a higher level of internal noise.
- At the individual level, increased deviation of the individual mental representations to the norm, and increased levels of internal noise levels, may correlate with smaller RP responses to smiled stimuli in WP1, and smaller facial/autonomic mimicry to smiled speech in WP3.

WP3 – Motor resonance to vocal emotion

This WP focusses on the mechanisms by which vocal smiles evoke automatic facial and autonomic reactions, and how these may be affected in ASD. Using a recent facial electromyography (EMG) paradigm combined with vocal smile transformations (Arias et al. 2018), we have shown that controls imitate smiles heard in speech with congruent zygomatic activity.

Objectives

- Adapt previous work on EMG responses (Arias et al., 2018) to children (partner 2) and ASD participants (partner 1), by simplifying/gamifying the task and testing implicit response paradigms.
- Extend previous work to also include autonomic mimicry using pupil size measurements during smiled-voice presentation.

- Study the impact of individual mental representations and internal noise, derived from WP2, on EMG and pupil responses.

Stimulus and procedure

Forty neutral sentences will be recorded by male and female native French speakers, and transformed using the smile and unsmile transformations defined as part of WP2, resulting in 40 neutral, 40 smile- and 40 unsmile-transformed sounds, for a total of 120 stimulus. Mean stimulus duration will be around 2 seconds.

Participants will be presented with a standard black-and-white image on the screen, as well as with a subset of these audio stimuli in a pseudo-randomized order (number to be adapted for feasibility in children and ASD participants). Four seconds after onset, they will be asked to rate to what extent each stimulus is pronounced with a smile using a visual analog scale ranging from 0 ("not smiling") to 10 ("a lot of smile"), while we record their zygomatic major (used to smile) and corrugator supercili (used to frown) muscles with facial EMG electrodes, and pupil dilation. The task will last about 12 minutes.

In a first experiment, all control and ASD participants will use the same stimuli, derived from WP2.

In a second experiment on a subset of 10 high-functioning ASD participants, sequences will include both the 120 generic control-group stimuli and 120 smiled stimuli created using each participant's own mental representations, also derived as part of WP2. This second experiment, conducted on a smaller group of participants but more extensive so as to allow testing for statistical significance at the participant level, will directly test whether individualized stimuli matched to the participant's mental representations generate stronger imitation reactions than a generic stimulus.

Population

The first experiment will use the same control and ASD population as WP1 and WP2 (see WP1 above). **The second experiment** will include a small (N=10) subset of ASD participants from the first sample, for whom mental representations (WP2) and pupil and EMG reactions (WP3) could be obtained with sufficient data quality in the first experiment.

Data analysis

EMG will be filtered with a 50Hz high-pass IIR filter and a 250Hz low-pass IIR filter, then segmented into 4s epochs. Epochs will be rectified and smoothed using a moving average function with a window of 300ms, and z-score normalized with respect to each trial's baseline. For each stimulus, a curve of pupillary variation relative to the 500ms baseline will be obtained after filtering of the data. The magnitude of the contagion effect will be calculated as the difference between pupil size to smiling and to neutral sentences (during the 3 seconds following sentence presentation). To compare smile and unsmile conditions at the group level (Experiment 1) and at the individual level (Experiment 2), mean EMG time series for both smile and unsmile will be analyzed with cluster permutation tests. In addition, to separate the contribution of stimulus acoustic features and co-occurring participants' rating to the muscle reactions, muscle activity will be modeled with Generalized Linear Mixed Models, using sound transformation (2 levels: smile vs unsmile effect), and participants ratings (ranging from 0 to 10) as predictors, and participant number and sound token as random factors (see Arias 2018 for a similar strategy).

Predictions

- In controls and ASD participants, EMG and pupil responses to smile stimuli may be degraded if individual mental representations diverge from the generic stimulus norm, or at higher levels of internal noise.

- In Experiment 1, ASD participants may have less behavioural outcomes (EMG, pupil) than controls to emotional stimuli, and this abnormality may correlate with abnormal encoding (WP1) or representations (WP2).
- In Experiment 2, ASD participants may show more facial/autonomic reactions to individualized stimuli than to generic stimuli, showing that impaired socio-emotional processing depends on perceptual representations. Note however that, in case reactions do not differ between individual and generic stimuli, the experiment will be equally conclusive in showing that mimicry impairment in ASD do not depend on abnormal perceptual representations, but rather on emotional contagion.

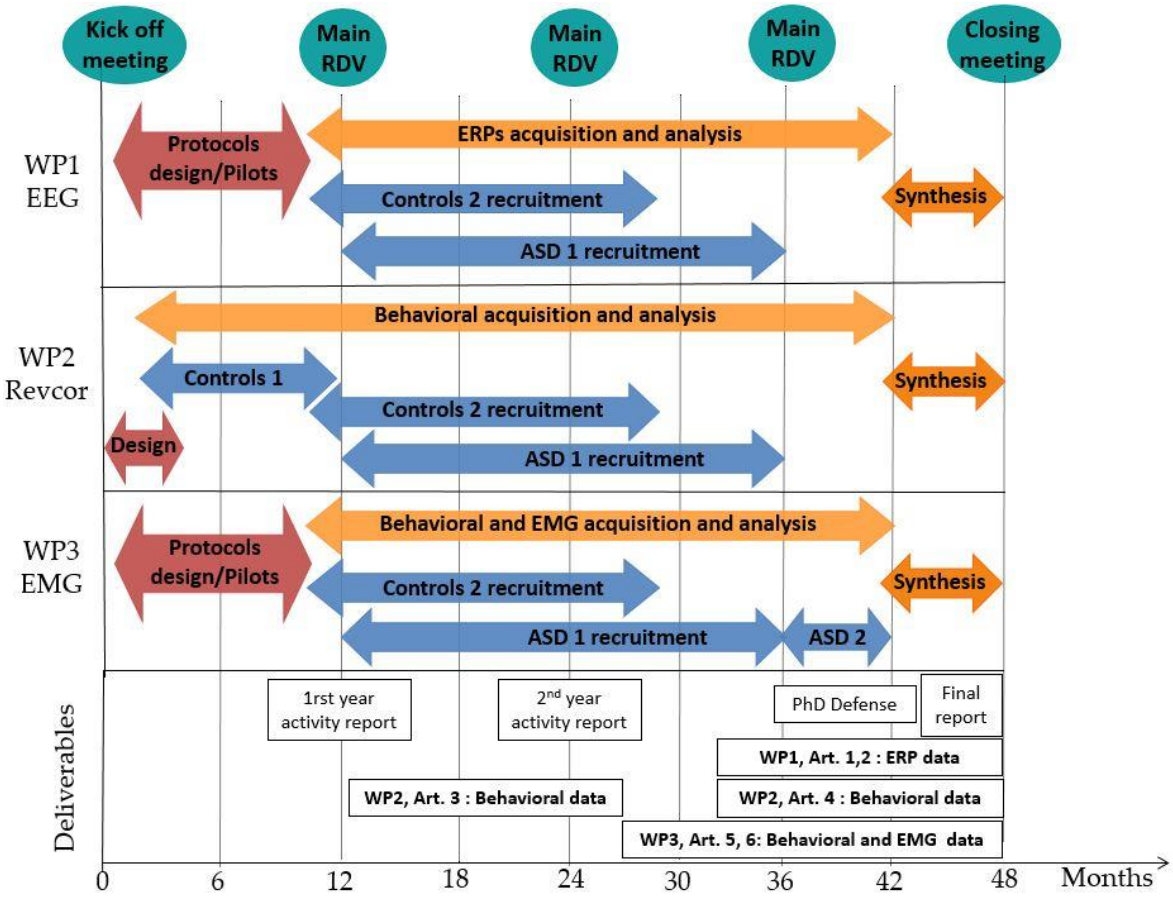

Fig. 6: General Gant chart: Work schedule will consist in the implementation of the study during year 1. Years 2 and 3 will be mainly devoted to the collection and analysis of the data, and year 4 will be dedicated to the final analyses of data and the dissemination of results (publications, conferences, PhD defenses).

Clinical Population (applies to WP1, WP2 and WP3)

Our behavioral and neurophysiological approach will be complemented by a thorough clinical characterization of the patients using ASD diagnosis gold standards but also specific clinical tools as described below, to establish potential bio clinical relationships

ASD participants' recruitment

ASD participants will mainly be recruited among patients attending units specialized in autism diagnosis and evaluation, i.e. the Centre de Ressource Autisme (CRA) for children and adults of Tours Val de Loire and the Centre Universitaire de Pédopsychiatrie (CUP) of the Tours University Hospital (partner 1). Patients will also be referred by Psychiatrists all over France.

Clinical characterization

Clinical assessment will be performed by psychiatrists and neuropsychologists from CRA and CUP, who are fully trained for autism diagnosis. Autism will be diagnosed according to DSMV criteria (APA, 2013) and confirmed by using the ADI-R/ADOS standardized diagnostic tools. Physical examination will be performed to evaluate metabolic, neurological or chromosomal disease. Patients with history of substantial neurological disorders or seizures, or presenting auditory deficit or abnormal EEG with either slow waves or epileptiform discharges will be excluded.

IQ of subjects with autism will be evaluated using mental age-appropriate Wechsler scales: WPPSI-IV and WISC-V for patients with developmental age under 17 and WAIS-IV for adults with intellectual abilities just below or within the normal range. Note that verbal and non-verbal skills will also be estimated in control participants using 4 selected subtests (Vocabulary, Similarities, Block design and Matrix reasoning) of the age-appropriate Wechsler scale. The severity of the non-social symptoms will be measured through the use of the Scale of Repetitive and Restrictive Behaviours (RRB) (Bourreau et al., 2009), a clinical tool which specifically evaluates behavioural manifestations related to resistance to change in autism. Socio-emotional skills will be specifically evaluated using the French versions of the Empathy Quotient (Baron-Cohen and Wheelwright, 2004) in adults and of the Child-EQ in children.

Ethical aspects and Protection of privacy

All of the experiments in humans mentioned here will be carried out under European and French national current regulations. Partner 1 has already obtained the ethical approval for both control and ASD, child and adult participants to perform behavioral, autonomic, EMG and EEG recordings (SCOPA - Etude neurophysiologique des processus sensoriels et cognitifs dans la pathologie - n° 2017-12-02, on 20/12/2017**;** and PROSCEA - Etude neurophysiologique des processus sensoriels et cognitifs chez l'enfant et l'adulte sains - 2017/23 –ID RCB: 2017-A00756-47, on 20/04/2017).

Partner 2 also has ethical agreement for reverse-correlation and EMG testing in healthy adult participants (INSEAD-Sorbonne Institutional Review Board n° 2015-12-02, renewed n° 2018-03-19). An amendment will be presented to perform such research in control children.

For all participants, data storage will be done anonymously, with a numeric code. Authorization of the CNIL will be asked for the controls. Patients' data will be entered in a clinical database developed and updated by the iBrain team and hosted by the CHRU of Tours, which already has authorisation from the CNIL. Once the study will be completed, data will remain in the laboratories for 15 years.

Risk management and fallback solutions

Long recruitment of ASD participants: Based on our previous experience, inclusion of participants with ASD can be quite time-consuming and is partly subjected to the consultation flow of our Clinical Centers. **Solution**: Duration of the project extended to 4 years.

Timing dependencies between WPs: Individualized stimuli in WP1 and WP3 require completion of WP2 before starting. **Solution**: Instead of using individualized stimuli, WP1 and WP3-Exp1 use generic stimuli derived from a low-risk control group (C1) to be acquired at the onset of WP2; responses to these stimuli will then be analyzed with respect to individual representations, when and if these are available. Only WP3-Exp2 at the outset of the project will use individual stimuli, and this only for a subset of participants for whom data has already been successfully acquired.

Incomplete data: Because of the difficulty to collect data in children and in ASD participants, some participants may only be able to complete some, but not all, of the experimental tasks needed for a complete comparison of WP1,2,3 data. **Solution**: Even if SEPIA claims an integrative view, individual experiments at each stage of the perception-action chain is innovative per se, and can be analyzed independently. In addition, stimuli in WP1 and WP3 (Exp1) do not depend on prior individual testing

in WP2 (because they are derived instead from control group C1). Only participants who completed WP2 and WP3-Exp1 will be recruited for WP3-Exp2.

No difference between ASD and controls in WP2: While we predict to use potential WP2 differences to explain abnormal ASD processing in WP1 and WP3, it is possible that ASD do not differ from controls on how they mentally represent auditory smiles. **Solution**: Not an issue. No difference found in WP2 provides a stringent control that none of the potential effects in WP1 and WP3 depend on abnormal perceptual representations, an important finding if it is the case. In addition, participants for WP3-Exp2 can be tested at the individual level even if there is not difference at the group level.

II. Organisation and implementation of the project

a. Scientific coordinator and its consortium / its team

Implication of the scientific coordinator and partner's scientific leader in on-going project(s)

Name of the researcher	Person.month	Call, funding agency, grant allocated	Project's title	Name of the scientific coordinator	Start - End
Marie Gomot	3	EU-H2020 Research and innovation program, grant agreement N° 731827	STIPED-Stimulation in Pediatrics https://www.stiped.eu/project/team/	M. Siniatchkin	2017-2021
	3	EU Innovative Medicines Initiative (IMI) grant agreement N° 777394	Autism Innovative Medicine Studies-2-Trials https://www.aims-2-trials.eu/	D. Murphy	2018-2022
Jean-Julien Aucouturier	48	ERC Starting Grant 335536	Cracking the emotional code of music (CREAM) http://cream.ircam.fr	JJ. Aucouturier	2014-2019
	15	AAP GENERIQUE 2017, Agence National de la Recherche	Retroaction Emotionnelle Faciale et Linguistique, et Etats de Stress Traumatiques (REFLETS)	C. Soladié (CentraleSupelec)	2017-2021

Project management

Marie GOMOT will be the project coordinator and will use 2 person.month for this activity of management during the 4 years period. During the project, the organization will be as follows:
- Every 3 months, conference calls with all participants will be scheduled and will aim to provide a summary report by each participant.
- A kick-off meeting, followed by yearly consortium meetings, will be organised in Tours and/or Paris. These meetings will allow us to evaluate the progress of the project for each WP and to highlight and solve any issues. A scientific and expense report will be sent to the scientific committee of the ANR in charge of project progress evaluation. The expense reports will be edited by the financial services of INSERM and IRCAM.
- At the end of the project, a final scientific and expenses report will be provided.

Coordinator: **Marie Gomot** (CRCN INSERM, UMR1253, Tours, involvement in the SEPIA project 60%) is a permanent researcher in Neurosciences (PhD, HDR) as well as a Psychologist (Professional diploma in clinical psychology). Her research addresses the main symptoms of ASD through the assessment of neural correlates of auditory, visual and emotion perception and discrimination. She uses fMRI and

EEG technics in typical children and adults and in people with autism, and in relationships with clinical data. These studies have lead in the publication of 45 papers in appreciated scientific journals: Brain, Neuroimage, Psychophysiol, SCAN, JADD, Autism, J Neurodev Disord, Molecular Psy.. Sum of time cited: 1675, h-index: 17. Marie has been PI or scientific leader of several research projects on ASD (ANR JCJC, PHRC, Orange Foundation..).

The consortium *involves* ***2 partners:***

Partner 1 Tours: The '**Autism**' group of the 'NeuroFunctional Psychiaty' team (coord. F. Bonnet-Brilhault) of the **UMR1253 iBrain**, **INSERM**, Université de Tours (lead. C. Belzung), is a multidisciplinary group of clinicians and scientists in complementary research fields (neurophysiology, psychiatry, neuropsychology, linguistics) with a strong expertise in the area of ASD. The group is integrated into the Child Psychiatric Department, Tours University Hospital, and collaborates with the local Autism Resource Centre, allowing local clinical assessment and brain investigations for research. The center receives approximately 200 children and 60 adults per year for diagnosis and intervention, which allows the recruitment of a large sample of participants with ASD with a thorough clinical assessment by a multidisciplinary clinical team (speech therapist, psychomotor therapist, psychologist, etc.). The group already has all the technical equipment needed to carry out the project. Due to the **expertise of the team and of the coordinator of SEPIA in clinical and neurophysiological research in ASD, explorations in patients will be performed in Tours**.

Partner 2 Paris**: STMS** (Sciences and Technology of Music and Sound, **UMR9912, CNRS/IRCAM/ Sorbonne Université)** is the country's only laboratory fully devoted to the science and technologies of music and sound, located in Institut de Recherche/Coordination en Acoustique et Musique (IRCAM) in Paris. It brings to the project high expertise in psychoacoustics and emotional speech. STMS will be **responsible for developing the audio methodologies of the project, as well as data collection in typical adults and children. Jean-Julien Aucouturier** (project involvement: 30%), neuroscientist, CR1 CNRS and PI of ERC StG CREAM (2014-2019), will coordinate STMS participation in the project.

b. Implemented and requested resources to reach the objectives

Partner 1: UMR1253, INSERM iBrain

The technical environment already comprises a fully equipped Eye tracking (SMI 500), physiological (Biopac) and EEG (Biosemi) lab, allowing for pupil, EMG, and ERP recordings.

Staff expenses

1 Doctoral position for 36 months (34 000*3years = **102 000** euros) to run EEG, EMG, pupillometry and behavioral experiments in patients with ASD and their matched typical controls

- 1 trained clinician to help for neuropsychological assessments of the patients (3000*6 months = **19 800** euros)

Instruments and material costs

- Furniture and Consumables (Biosemi complementary modules, electro gel, EMG electrodes, caps...): **9 000** euros
- 1 laptop for the purpose of experimental design and data analysis: **1 500** euros
- One PC workstation dedicated to EEG data measurements and analysis: **2 000** euros

Outsourcing / subcontracting.

- Software licenses: **1 000** euros
- Publication fees (2000 euros*4 = **8 000** euros)
- Insurance for 160 participants: **2 000** euros

- Travels costs and living expenses of ASD patients and their families: **3 000** euros
- Participation fees for adult subjects: **1 400** euros
- Small gifts for children: **1 100 euros**

General and administrative costs & other operating expenses

- Travel costs for diffusion of the results at international conferences for 2 people in the final 2 years (2200 euros*2 persons * 2 years = **8 800** euros)
- Meeting of the consortium: 3 during year 1, then once a year (**1 500** euros)
- Travel costs for inter-WP data analyses (**700** euros).

Partner 2: STMS, UMR9912, CNRS/IRCAM/UPMC

Technical environment consists of a fully equipped EEG/EMG (BrainProducts Actichamp), Eye tracking (Tobii) lab and audiometric cabins (IAC) for psychophysics.

Staff expenses

- 1 post-doctoral position for 20 months to adapt and run reverse-correlation experiments in young healthy participants and analyze the corresponding data (2 to 4 years experienced, 54 630 euros*20months = **91 060** euros)
- Permanent staff included in consolidated costs: 102 200 euros (Total staff: 193 260 euros)

Instruments and material costs

- 1 laptop for the purpose of experimental design and data analysis: **1 500** euros
- Auditory recording: **1 000** euros

Outsourcing / subcontracting

- Participation fees for adults subjects (INSEAD) (**1 500** euros)
- Publication fees (2000 euros*2 = **4 000** euros)

General and administrative costs & other operating expenses

- Travel costs for diffusion of the results at international conferences for 2 persons*2 years = **8 800** euros
- International Workshop organization: **5 000** euros.

AAPG2019	SEPIA		Funding instrument PRC
Coordinated by:	Marie GOMOT	Duration 46 months	Requested Funding 348.7K€
Scientific evaluation committee CES37 Neurosciences Intégratives et Cognitives			

Requested means by item of expenditure and by partner

		Partner UMR1253, INSERM iBrain	**Partner** STMS, UMR9912, CNRS/IRCAM/UPMC
Staff expenses		121 800	91 060
Instruments and material costs (including the scientific consumables)		13 500	2 500
Building and ground costs		-	-
Outsourcing / subcontracting		15 500	5 500
General and administrative costs & other operating expenses	Travel costs	11 000	13 800
	Administrative management & structure costs**	12 944	132 942
Sub-total		174 744	348 002
Funding rate/ requested funding		100% / **174 744**	50% / **174 001**
Total funding		**348 745**	

III. Impact and benefits of the project

Scientific and Clinical Impact

The anticipated outcomes of the project are unique and of major interest to advance the current understanding of the physiopathological mechanisms of ASD, with the ultimate goal of improving therapeutics. The project's joint exploration of emotional and cognitive perception-representation-action loop with a methodological approach combining ERP, EMG, pupillometry and psychophysics, will help to better understand the brain mechanisms underlying socio-emotional perception in ASD and thus have important implications at both theoretical, methodological and clinical levels.

1) At the **theoretical level**, results will provide empirical grounds on adaptive behaviors, as it could help moving edges of the current understanding of the perception-representation-action chain for both sensory and emotional information.

2) At the **methodological level**, the project will provide new open-source tools for stimulus preparation, data collection and data analysis aiming to facilitate the use of reverse-correlation paradigms. This will allow researchers and clinicians in the community to harvest their potential to study individual differences in a range of clinical populations beyond autism.

3) Finally, at the **clinical level**, results of this project will allow identifying specific biomarkers and will open new lines of research for subsequent behavioral cognitive therapies. Understanding deficits at any step of the emotional or non-emotional perception-representation-action chain may indeed contribute, in the long term, to identify new targets for clinical and educational interventions tailored to each subgroup of patients (e.g. re-educate mental representations, to either impact automatic change detection up-stream, or spontaneous social-response behavior down-stream).
In this way, project SEPIA fits with the ANR strategic priority to promote research in 'Autisme au sein des troubles du neurodevelopment''.

Clinical and industrial valorization

Potential biomarkers will be evaluated at the outset of the project by seeking additional funding for a clinical trial via the Ministry of Health's PHRC program.
In addition, any innovation in e.g. computer-based rehabilitation tools for ASD resulting from the project will be considered for IP protection, proof-of-concept and startup development, with accompaniment provided by programs such as CNRS Innovation and INSERM Transfer. Valorization efforts will be helped by the fact that Partner 2 is already the co-founder of a startup in the domain of emotional voice transformation, and that the smiling voice transformation used in the project is already patented (*Method and Apparatus to modify voice timbre by shifting the formants of spectral envelopes, EP2018/053433, CNRS/IRCAM/Sorbonne Université*). Conditions favoring the technological transfer from and between partners will be made explicit in the project's consortium agreement.

Promotion of results from the project will be performed through:

- Scientific publications in renowned journals in the following fields: psychiatry, psychophysiology, neurophysiology, neuroimaging, cognitive and affective neurosciences (JADD, Autism, Molecular Autism, Am J Psych, Brain, Neuroimage Clinical, SCAN, Neuropsychologia…),
- Oral and Poster presentation in targeted national and international scientific conferences (IMFAR, HBM, MMN, ESCAN, ICON, IOP, SPR,…).
- Existing collaboration of the consortium's participants with external researchers who will be invited for talk and discussions (Chakrabarti B, Golan O, Escera C, Schyns P, Gosselin P, Belin P, Kotz S…).
- Appropriate structures from INSERM, University of Tours, IRCAM and CNRS will publish press releases to publicize the results.
- Presentation to general audiences through several scientific popular events such as 'Semaine du cerveau' and 'Fête de la Science'.
- Organization in Paris of an international workshop on the clinical use of reverse-correlation (Partner2).

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