Profiling cognition in fragile X syndrome: A psychophysiological and neuropsychological approach
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Chapter 6

Summary and discussion
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The primary objective of this thesis was to provide a detailed characterization of cognitive functioning in FXS and to investigate its underlying information processing characteristics. Results of these investigations could further our understanding of the basic information processing characteristics that go astray in FXS and lead to important hypotheses on the causal neural mechanisms that can account for the cognitive and behavioral abnormalities. We first characterized the cognitive profile of relative strengths and weaknesses in cognitive abilities in adult males with FXS, using a battery of tests measuring cognitive abilities in verbal, non-verbal, memory and executive functioning domains (Chapter 2). This cognitive profile was subsequently used as starting point for in-depth analysis of (1) the underlying information processing characteristics in the attentional domain (Chapter 3), as well as (2) the basic information processing characteristics associated with stimulus perception and discrimination in the FXS brain (Chapters 4 and 5). Results of these investigations could provide a link between cognitive deficits and their possible underlying neurobiological mechanisms.

6.1 The cognitive profile in fragile X syndrome
Cognitive functioning in FXS has been widely investigated. However, some key issues regarding profiling relative strengths and weaknesses in cognitive functioning were unexplored. For example, cognitive functioning in FXS is subject to high levels of variability (Dykens, Hodapp, & Leckman, 1987), which raises the important question whether cognitive profiles are similar for individuals of various performance levels. In addition, in chapter 2, we addressed the critical issue whether the use of the frequently employed verbal mental age reference measure (i.e., receptive vocabulary) could bias the interpretation of the cognitive profile in terms of relative strengths and weaknesses. To this end, we contrasted cognitive performance to both a verbal and non-verbal mental age reference measure.

Results of the Chapter 2 study corroborated previous findings (Dyken et al., 1987; Maes, Fryns, Van Walleghe, & Van den Berghe, 1994) by showing
that cognitive performance is particularly weak on measures of reasoning and per formal abilities confined to abstract item content. In contrast, visuo-perceptual recognition and receptive vocabulary were relative strengths in FXS cognitive functioning. Model-based cluster analyses furthermore revealed that this pattern of findings was similar for FXS males of different overall performance levels/IQs. Although future investigations should aim to replicate similar findings for domains of memory and executive functioning, our current results strengthen the notion that cognitive functioning in FXS males can be characterized by a profile of relative strengths and weaknesses in cognitive functioning that is similar for FXS individuals of various levels of performance.

In addition, FXS males exhibited a pronounced deficit in verbal short-term memory. By using both non-verbal and verbal mental age reference measures, we were able to demonstrate that the significance of this discrepancy between verbal and visual short-term memory could only be observed when contrasting short-term memory abilities with the non-verbal reference measure. Also, for the remaining sub-domain analyses, the choice of an appropriate reference measure revealed to be critically important in examining cognitive profiles. That is, when compared to the verbal mental age reference, most cognitive abilities showed as relative weakness, whereas comparison with the non-verbal mental age reference exposed more subtleties in relative strengths and weaknesses in cognitive performance. In this regard, the use of receptive vocabulary as a single reference measure will result in an overabundance of cognitive weaknesses in FXS individuals. This in turn may compromise identifying relative strengths and weaknesses in cognitive performance.

Together, the findings that emerged from this study revealed that adult FXS males can be characterized by an overall impairment in cognitive functioning, based on mental age level performance. In addition, those cognitive abilities with a high demand on executive control seemed to be more significantly impaired than perceptual functions. However, based on the findings reported in the ERP studies (Chapters 4 and 5), we provide evidence that information processing in the FXS brain is already compromised during the
bottom-up stages of information processing, which could impact on the later, cognitive stages of information processing.

6.2 **Attentional set-shifting in simple and complex stimulus environments**

To complement the cognitive profiling study (chapter 2), we next characterized attentional set-shifting ability in FXS males using the IED from the CANTAB test battery. As each subsequent stage on the IED imposes a higher demand on attentional control, we were able to investigate in more detail those cognitive processes that contribute to the alleged attentional control deficiencies in FXS. In order to interpret results in terms of syndrome-specific signatures, we compared IED performance of FXS males to that of three control groups, comprising typically developing adults and children matched on chronological and mental age, respectively, as well as individuals with Down syndrome matched on both chronological and mental age.

Based on overall IED stage performance, a significant proportion of the FXS participants already failed *before* the crucial intra- and extra-dimensional set-shifts. This finding may suggest that the key weakness characterizing cognitive flexibility in FXS is not shifting attentional set *between* stimulus dimensions, but can be traced back to more basic reversal learning. Indeed, with a novel approach to investigate IED stage performance in terms of *repetition, maintenance, and discrimination errors*, we were able to show that attentional set-shifting ability in FXS males differed from the control groups based on a significant impairment in reversal learning, as a result of enhanced repetitive decision-making. Although feedback indicated that a formerly correct stimulus now had become incorrect, FXS males continued to respond to this previously reinforced stimulus. Interestingly, this increased repetitive behavior during reversal learning was particularly observed when faced with simple stimulus configurations.

A potential explanatory mechanism of this enhanced repetitive decision-making could be the *perseverative* responding due to a failure to disengage attention from a previously reinforced, but now incorrect stimulus.
Another potential, but contrasting, underlying mechanism is *learned irrelevance*, which refers to reduced attention directed towards a particular stimulus that has proven to be irrelevant (Mackintosh, 1975). For example, FXS males may have a specific weakness in reorienting attention towards a stimulus for which a former association with irrelevance exists. A limitation in the IED experimental design is that perseverations and learned irrelevance cannot be accurately disentangled. Therefore, future studies should preferably design their experimental paradigms in a way that allow to investigate these cognitive phenomena separately.

Besides repetitive decision-making, FXS males also showed enhanced distractibility to irrelevant stimuli. In contrast to all control groups, FXS males exhibited greater difficulty with completing the compound discrimination stages, in which distractor stimuli were introduced from a non-reinforced, novel stimulus dimension. When presented with this more complex stimulus configuration, FXS males engaged in increased random search behavior, which was particularly observed during the reversal of the compound discrimination stage.

This increased distractibility to irrelevance could possibly be explained by an underlying deficiency in stimulus perception, compromising stimulus discrimination, and perhaps, novelty processing. In more detail, increased neural and behavioral sensitivity to the perception of sensory stimulation has been widely described in humans with FXS (Castrén, Paakkonen, Tarkka, Ryynanen, & Partanen, 2003; Ferri et al., 1994; Frankland et al., 2004; Hessl et al., 2009; Miller et al., 1999; Rojas et al., 2001), as well as in the *fmr1* knockout mouse (Chen & Toth, 2001; Frankland et al., 2004; Moon et al., 2006). In particular, neural hyperexcitability has been demonstrated in the FXS brain by augmented event-related brain potentials to auditory stimuli (i.e., tones) (Castrén et al., 2003; Rojas et al., 2001). Also on a behavioral level, FXS males are hypersensitive in loud or crowded environments (Hagerman & Hagerman, 2002), possibly a reflection of aberrant stimulus perception in the brain. This increased neural activity to incoming stimuli may hinder efficient downstream information processing necessary to distinguish between relevant and
irrelevant stimuli. Indeed, by investigating the pre-attentive and attentive stages of stimulus perception and discrimination in chapters 4 and 5, we found support for this notion.

6.3 Stimulus processing in the FXS brain: evidence from passive and active information processing paradigms

The investigations in both Chapters 2 and 3 demonstrated that cognitive and attentional functioning is particularly impaired for those functions with a high demand on attentional or executive control. However, based on increased distractibility to irrelevant stimuli (Chapter 3), as well as prior evidence of enhanced sensitivity to stimulus perception, it could be speculated that information processing in FXS is already compromised during the early (pre-attentive) stages of information processing. These alleged early stimulus perception abnormalities could result in a cascade of information processing deficiencies, compromising efficient decision-making and goal-directed behavior (Nieuwenhuis, Aston-Jones, & Cohen, 2005; Polich, 2007).

In Chapter 4 we investigated passive stimulus detection and discrimination in the FXS brain using the passive variety of the oddball paradigm in which infrequent (deviant) tones were embedded in a sequence of frequent (standard) tones. Results corroborated the previously reported N1 augmentation to stimulus detection (Castrén et al., 2003; Rojas et al., 2001) and revealed the novel finding that N1 amplitude did not differentiate between standard and deviant tones in FXS males. More specifically, in control participants we observed significantly larger N1 amplitudes to deviant than standard tones, whereas in FXS males this difference was absent. Normally, stimulus repetition leads to a decrement in N1 generation, a process referred to as habituation (May et al., 1999; Sable, Low, Macllin, Fabiani, & Gratton, 2004). The current data suggest that this habituation to stimulus repetition is impaired in FXS males.

Dishabituation to stimulus repetition has been previously reported in FXS children (Castrén et al., 2003) and could be related to elevated levels of neural excitability resulting from imbalanced excitatory (glutamatergic) and
inhibitory (GABAergic) neurotransmission (Bear, Huber, & Warren, 2004; D’Hulst et al., 2006) which in turn compromises the efficiency of pre-attentive change detection mechanisms in the FXS brain. Indeed, results showed that the pre-attentive change detection mechanism (MMN) was significantly attenuated in FXS males. Interestingly, this MMN attenuation was followed by augmented N2b and reduced P3a activity, which are ERP components associated with the allocation of attentional resources to salient or novel stimuli (Escera, Alho, Winkler, & Näätänen, 1998; Escera, 2007). The observed reduction of MMN amplitude is likely a resultant of impaired sensory stimulus representation, subsequently compromising the efficient triggering of attentional resources to a potential important event, as well as the active inhibition of information processing related to irrelevant stimuli (Polich, 2007).

This notion of a cascade of information processing deficiencies as a potential explanation for impaired decision-making at the behavioral level was supported by our findings from the selective attention study described in Chapter 5. On both auditory and visual tasks, we found an augmentation of the N1 response to standard stimuli, which was followed by a significant reduction in P3b activity to deviant stimuli. At the behavioral level, FXS participants showed impaired performance on both auditory and visual tasks, with a considerable proportion of participants performing below chance level on the auditory task. Results furthermore showed that, in the FXS group, variation in P3b activity to deviant stimuli best explained performance on the oddball tasks. That is, larger P3b difference scores were related to better task performance. As P3b activity is posited to reflect the outcome of a decision-making process in the brain (Nieuwenhuis et al., 2005), it could be argued that deficient information processing at the network level underlies impairments observed at the behavioral level.

Interestingly, the observation of auditory vs. visual performance discrepancies on the oddball task corresponded to modality differences in information processing. That is, those participants with above-chance level performance showed larger P3b activity in response to visual deviants relative to auditory deviants. In controls, however, both behavioral and ERP indices
were similar between modalities. Although the visual stimuli may have been more appealing (i.e., attention grabbing) or salient than the auditory stimuli used in the Chapter 5 study, it could be argued that due to FMR1 silencing, information processing in the auditory modality is more severely affected than in the visual modality. This is in line with the auditory vs. visual short-term memory discrepancies found in the Chapter 2 study, as well as with a host of studies reporting elevated arousal levels in response to auditory stimulation (Castrén et al., 2003; Chen & Toth, 2001; Frankland et al., 2004; Hessler et al., 2009; Moon et al., 2006; Rojas et al., 2001).

6.4 Concluding remarks

Taken together, the combined psychophysiological and neuropsychological approach in the current thesis has contributed to our understanding of how certain aspects of cognitive dysfunction in FXS may result from abnormalities in underlying information processing characteristics. Particularly, results from the ERP studies add an important dimension to explaining FXS cognitive dysfunction in terms of a primary deficiency in top-down, executive control. Although perceptual functions may seem to comprise relative strengths at the behavioral level (Chapter 2), the pre-attentive and attentive change detection studies (Chapters 4 and 5) have provided clear evidence of deficient lower-level information processing. Based on these findings we can conclude that although cognitive functioning in FXS may be characterized by executive control deficiencies at the behavioral level, lower-level perceptual impairments likely contribute to these cognitive deficits. More specifically, our results suggest that during active selective attention in the auditory modality, appropriate coupling between sensory change detection and active decision-making processes seems absent in FXS information processing. That is, in the control group we found that an increase in sensory change detection (N1 and P2 activity) was related to an increase in the active triggering of attention (N2b and P3b activity), whereas this correlation between bottom-up and top-down information processing mechanisms was absent in FXS males. However, in our passive change detection study (Chapter 4) we did not find a direct association between a
sensory change detection mechanism (MMN) and the involuntary triggering of attention (P3a). This may suggest that the alleged fine-tuning between sensory and attentive information processing (Näätänen, Kujala, & Winkler, 2011) is more influenced by top-down factors, as is the case during active decision-making.

In terms of unraveling syndrome-specific profiles of cognitive function, the question remains whether these lower-level information processing impairments are characteristics for the FXS etiology. For example, P3b attenuation has been reported in a variety of other neurodevelopmental disorders, such as Rett and Prader-Willi syndrome (Sable et al., 2004; Stauder, Smeets, van Mil, & Cursfs, 2006; Strauss, Sherman, & Spreen, 2006). Although the MMN has been less frequently investigated in neurodevelopmental disorders, evidence also suggests impaired functioning of this pre-attentive change detection mechanism in autism, ADHD, and non-syndromic intellectual disability (Dunn, Gomes, & Gravel, 2008; Ikeda, Hashimoto, Hayashi, & Kanno, 2009; Ikeda, Okuzumi, Hayashi, Hashimoto, & Kanno, 2000; Kemner et al., 1996). Therefore, impairments during early stages of information processing may not be specific to FXS, but comprise a more general functional outcome of abnormal brain development. In contrast, N1 augmentation in both auditory and visual modalities may be most characteristic of the information processing deficiencies in FXS, since in a variety of other neurodevelopmental disorders (e.g., autism, ADHD, Down syndrome) an attenuation of this ERP component is observed (Barry, Johnstone, & Clarke, 2003; Bruneau, Roux, Adrien, & Barthelemy, 1999; Pekkonen, Osipova, Sauna-Aho, & Arvio, 2007). As the N1 is argued to reflect the pre-attentive extraction of the characteristics (e.g., intensity) of a detected stimulus (Näätänen & Picton, 1987), it could be argued that stimulus perception per se is not the problem, but the problem lies in the extraction of its specific properties.

From our results it appears that FXS males experience a specific difficulty with the passive or involuntary extraction of deviant or novel information from a continuous stream of stimuli within the environment (Näätänen, 2008; Näätänen & Escera, 2000; Näätänen et al., 2011; Näätänen,
Paavilainen, Rinne, & Alho, 2007). Based on the hyperexcitable state of sensory information processing, as well as the syndrome-specific difficulties in ignoring irrelevant stimuli (Chapter 3), it could be argued that the pre-attentive switching between bottom-up and top-down attentional networks (Crottaz-Herbette & Menon, 2006; Fox, Corbetta, Snyder, Vincent, & Raichle, 2006; Menon & Uddin, 2010) is impaired in FXS. In more detail, it has been suggested that efficient goal-directed behavior is enabled by the dynamic switching between a default mode network and a central executive network, in which a saliency network operates as a so-called ‘neural interface’ between these two networks to filter out relevant stimuli from the stream of irrelevant stimuli (Menon & Uddin, 2010). Based upon the observed neural hyperexcitability observed during early information processing, it could be argued that due to impaired functional connectivity in the FXS brain (Belmonte & Bourgeron, 2006), this saliency network fails in the dynamic switching between the default mode and central executive networks. That is, due to the alleged dishabituation to stimulus repetition, important stimuli can be less efficiently extracted from a continuous stream of information, probably resulting in noisy network-level decision-making. This speculative account of attentional function at the network-level requires further investigation in future studies.

6.5 Future prospects

Although the investigations in this thesis have contributed to our understanding of the underlying mechanisms of cognitive deficits in FXS, the top-down profiling approach (see Figure 1, Chapter 1) may be extended by promising lines of research. A first recommendation concerns investigating developmental trajectories of information processing in FXS. Although the current findings may be representative for adult FXS males, different results on cognitive information processing may be observed in younger and older FXS individuals. Additionally, in order to reveal ‘neurocognitive signatures’ specific for FXS, these investigations should also include other neurodevelopmental disorders, matched on general intelligence. This way, differences can be attributed to etiology, rather than general intellectual impairment, and the
results derived from these studies will provide a more accurate understanding of the gene-brain-cognition relationship in FXS.

Another interesting avenue for further research concerns delineation of the observed augmentation of sensory brain activity in FXS males. In the current thesis, the enhanced N1 and P2 activity during stimulus detection in the FXS brain was hypothesized to reflect a failure of neuronal habituation, presumably due to an imbalance in excitatory and inhibitory activity in the central nervous system. Abnormalities in the excitatory mGluR and inhibitory GABAergic systems have been well established (Bear et al., 2004; Huber, 2007) and deficiencies in these neurotransmitter systems may contribute to the behavioral symptoms observed in FXS individuals (Heulens, D'Hulst, Braat, Rooms, & Kooy, 2010; Heulens & Kooy, 2011b). For example, the experimentally validated “mGluR” theory states that increased signaling through group 1 glutamate receptors is responsible for the clinical symptoms (i.e. anxious behavior and epileptic activity) observed in FXS (Bear et al., 2004). Interestingly, by targeting the GABA_B receptor using arbaclofen, a GABA_B receptor agonist, diminishment of excessive glutamate signaling and a subsequent reduction of clinical symptoms was observed in both the fmr1 knock-out mice, as well as in individuals with FXS (Heulens & Kooy, 2011b). Putatively, pharmacological reduction of the presumed neural hypersensitivity could contribute to more efficient information processing in the FXS brain.

Another promising avenue for further research is the study of event-related brain dynamics (e.g., oscillatory cortical activity), and the imaging of structural and functional neural networks (e.g., with DTI, MRI, fMRI, EEG, MEG, and resting-state brain activity). In contrast to the work on typical development, surprisingly few investigations have studied development of structural and functional brain networks in atypical development. A possible explanation for this lack of research refers to the complications that are experienced when intellectually low-functioning individuals enter a brain-imaging scanning device, or when an EEG electrode cap is placed on their heads. Frequent obstacles to successful measurements include exaggerated
movement or anxious behavior, thereby prohibiting lengthy neuroimaging sessions.

In particular, resting-state fMRI/EEG may offer an interesting framework for studying the structural and functional characteristics of brain development in both typical and atypical populations (Uddin, Supekar, & Menon, 2010). The advantage is that brain function can be examined independent of task performance, which allows collecting informative datasets in just a few minutes. Patterns of resting-state brain activity have shown to be highly informative for investigating the development of large-scale brain networks (Douw et al., 2011; Fox & Raichle, 2007; Greicius, Supekar, Menon, & Dougherty, 2009; Stam, 2004). Using fMRI, spontaneous fluctuations in the BOLD response can be correlated between different brain regions to provide an index of functional connections (Fox & Raichle, 2007), whereas in EEG, coherence between electrodes can be calculated and/or network analysis (e.g., based on graph theory) can be performed to characterize the development of structural and functional brain networks (Bullmore & Sporns, 2009; Stam, 2004). These methods of analyzing resting-state brain activity can shed light on potentially disrupted cortical networks in neurodevelopmental disorders at any point in development.

In normal development, the analysis of resting-state brain activity has complemented theoretical views of brain development (Johnson, 2001; Johnson, 2011) by showing a transition of short-range brain connectivity networks observed in children into the advancement of long-range connectivity patterns as observed in adults (Boersma et al., 2011; Fair et al., 2007; Kelly, Uddin, Biswal, Castellanos, & Milham, 2008). Furthermore, it has been shown that specific functional neural networks, such as sensorimotor systems, precede the development of other neural systems, for example those underlying higher-level information processing (Chugani, Phelps, & Mazzotta, 1987; Durston et al., 2006; Kelly et al., 2009; Lin et al., 2008). Importantly, these findings on structural and functional brain development derived from typical development can be used as a model for interpreting trajectories of atypical brain development, such as in FXS. Currently, resting-state EEG data is being
analyzed in adult FXS males to reveal connectivity patterns of functional brain networks (Van der Molen, Van der Molen, Ramakers, & Stam, 2011). These results on ‘Small-World’ networks could then be correlated to measures of cognitive performance to study the integrity of these functional brain networks. For example, in normal development, the observed ‘path length’ in these modeled neural networks has proven to be a reliable measure of intelligence (i.e., shorter path length corresponding to higher intellectual performance levels) (Langer et al., 2011; Van den Heuvel, Stam, Kahn, & Hulshoff Pol, 2009). Based on the well-defined neurobiological background of FXS (i.e., immature cortical network development), resting-state analyses of brain activity will undoubtedly yield promising results.

In closing, I would like to argue that these proposed avenues for further research should not be studied in isolation. In order to truly understand the impact of FMRP depletion on brain development and cognitive functioning, it may be highly informative to correlate results on, for example, ‘Small World’ neural networks derived from resting-state brain activity with the patterns of GABAergic receptor expression in the FXS brain. Currently, GABAergic receptor expression is being analyzed in the brains of male adults with FXS using positron emission tomography (Heulens & Kooy, 2011a). Within an ideal multidisciplinary framework, the observed individual differences derived from these investigations could then be linked to cognitive performance levels. Importantly, when studied at different points in developmental time, a true understanding can be derived of the consequences of single-gene silencing on cognitive development.